

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

SDH mutations in tumorigenesis and inherited endocrine tumours: lesson from the pheochromocytoma-paraganglioma syndromes

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/57132> since

Published version:

DOI:10.1111/j.1365-2796.2009.02111.x

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Published in final edited form as:

J Intern Med. 2009 July ; 266(1): 19–42. doi:10.1111/j.1365-2796.2009.02111.x.

SDH MUTATIONS IN TUMOURIGENESIS AND INHERITED ENDOCRINE TUMOURS

Pasini Barbara¹ and Constantine A. Stratakis²

¹Department of Genetics, Biology and Biochemistry, University of Turin, Via Santena 19 - 10126 Turin TO Italy, barbara.pasini@unito.it

²Section on Endocrinology & Genetics, Program on Developmental Endocrinology & Genetics, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892

Abstract

A genetic predisposition has been recognized for paragangliomas and adrenal or extra-adrenal pheochromocytomas was recognized years ago. Well known syndromes associated with an increased risk of pheochromocytoma include Von Hippel Lindau disease, multiple endocrine neoplasia type 2, and neurofibromatosis type 1 and are discussed elsewhere. The study of inherited predisposition to head and neck paragangliomas led to the discovery of three genes encoding subunits of the succinate dehydrogenase (SDH) enzyme (*SDHB*, *SDHC* and *SDHD*) thus opening an unexpected connection between mitochondrial tumour suppressor genes and neural crest-derived cancers. In this review we summarize the most recent knowledge about the role of SDH in tumorigenesis, including spectrum and prevalence of mutations, related phenotypes, and the biological hypotheses attempting to explain tumorigenesis, as well as current questions and ongoing research.

Keywords

Succinate dehydrogenase; neuroendocrine tumours; tumour suppressor genes

Introduction

Hereditary susceptibility to paragangliomas, mainly of the head and neck region, was recognized at least two decades ago and led to the identification through linkage analysis of three loci on chromosome 11 and 1, named PGL1 on 11q23 [1–4], PGL2 on 11q11.3 [5, 6] and PGL3 on 1q21–23 [7, 8]. Co-occurrence of both paragangliomas and pheochromocytomas was also well recognized [9]. Following the discovery of *SDHD* [succinate dehydrogenase (SDH) subunit D gene, OMIM 602690] as the gene responsible for PGL1 in familial head and neck paragangliomas [10], it was thereafter recognized that two other subunits of this mitochondrial enzyme, *SDHC* (PGL3, OMIM 602413) and *SDHB* (PGL4, 1p36, OMIM 185470) were associated with heritable pheochromocytoma and/or paraganglioma [11, 12]. To date, the gene for PGL2 has not been identified.

Corresponding author PASINI Barbara, University of Turin, Department of Genetics, Biology and Biochemistry, Via Santena 19 - 10126 Turin (TO) - Italy, barbara.pasini@unito.it, phone: +39-011-6334479, fax: +39-011-6335181, mobile: +39-335-8338548.

Conflict of Interest Statement

The authors declined any conflict of interest.

Parangangliomas and pheochromocytomas

Paranganglia comprise a diffuse neuroendocrine system dispersed from the middle ear and the skull base to the pelvic floor. They play an important role in the homeostasis against hypoxia, bleeding, cold and hypoglycaemia. Non-chromaffin paragangliomas (PGLs) are usually benign and slow-growing tumours of the parasympathetic ganglia with an incidence of roughly 1:30.000 – 1:100.000 in the general population. They are more frequently located in the head and neck region (HNPGs) at the carotid bifurcation (carotid body tumour), along the vagal nerve, in the jugular foramen and in the middle ear space. Less common sites are close to the larynx, thyroid, urinary bladder and the upper mediastinum. Known risk factors for HNPGs include conditions associated with chronic hypoxia such as living at a high altitude, respiratory and heart diseases with chronic arterial hypoxaemia and related states. However, in 7–10% to 50% of cases a genetic predisposition has been suspected based on positive family and/or development of bilateral or multiple primary tumours [13–16]; more recently the proportion of tumors due to an inherited predisposition has been identified to be close to 35% [17].

The sympatho-adrenal system includes the adrenal medulla, the Zuckerkandl body at the root of the inferior mesenteric artery, and a series of chromaffin cells clustered in the paravertebral chain, kidney and liver hilum, aortic bifurcation, bladder and mediastinum. Pheochromocytoma (PHEO) arises in 80–90% of cases within the adrenal medulla (more frequently the right) while extra-adrenal PHEOs (more properly called “parangangliomas”) are described in 10–20% of cases. Hypertension and other symptoms of increased catecholamines secretion occur in approximately 90% of cases and tumours are malignant at first operation in 4–7% of cases. The life-time risk of metastases seems greater for extra-adrenal PGLs (23.9% vs. 6.7% for adrenal PHEOs), younger patients and larger tumours [18–20]. Adrenal PHEO, often bilateral, is a feature of the inherited cancer syndromes multiple endocrine neoplasia type 2 and Von Hippel Lindau disease and can occur in 0.1–5.7% of neurofibromatosis type 1 patients [21, 22]. Recently, additional genes/loci predisposing to PHEO have been recognized on chromosome 1p36 (*KIF1B*) [23, 24], 2q and 6p [25] but their causative role is still to be confirmed.

Succinate dehydrogenase and encoding genes

SDH or succinate-ubiquinone reductase is the complex II of the mitochondrial respiratory chain located in the mitochondrial matrix [26]. SDH couples the oxidation of succinate to fumarate in the Krebs cycle with electron transfer to the terminal acceptor ubiquinone in a way to prevent formation of potentially dangerous reactive oxygen species (ROS) [27]. SDH is an enzyme complex composed by four subunits encoded by four nuclear genes (*SDHA*, *SDHB*, *SDHC* and *SDHD*). *SDHC* (cybL, 15 kDa) and *SDHD* (cybS, 12 kDa) subunits are hydrophobic and provide membrane anchor and the binding site for ubiquinone. *SDHA* (flavoprotein, 70 kDa) and *SDHB* (iron-sulfur protein, 27 kDa) are hydrophilic with the former involved in substrate binding and oxidation and the latter in electron transfer [27]. Both the *SDHB* and the *SDHC* genes are located on chromosome 1, the short and long arm respectively. The *SDHC* gene spans 50.3 kb and contains 6 exons transcribed in an mRNA of 2858 nucleotides (long isoform) corresponding to the precursor peptide of 169 amino acids. The *SDHB* gene spans 35.4 kb and contains 8 exons transcribed in an 1161 nucleotides (nt)-long mRNA encoding a protein of 280 amino acids. The *SDHD* gene located on 11q23.1 spans 8.9 kb and contains four exons transcribed in an 1313 nt-long mRNA encoding a protein of 159 amino acids. Finally *SDHA* lies on the short arm of chromosome 5 (5p15) and it is composed by 15 exons spread in a genomic region of 38.4 kb. Its mRNA, 2405 nucleotides long, is transcribed in a protein of 664 amino acids. While homozygote germline mutations affecting the *SDHA* gene cause Leigh syndrome, a subacute necrotizing encephalomyelopathy during infancy [28–30], *SDHD*, *SDHB* and *SDHC*

heterozygous mutations cause a genetic predisposition to HNPGLs and adrenal / extra-adrenal PHEOs [10–12] called “paranglioma-pheochromocytoma syndrome”. This inherited cancer predisposition is transmitted in an autosomal dominant fashion with age-dependent and incomplete penetrance. However, for loci located on chromosome 11q (*SDHD* and *PGL2*) a parent-of-origin effect is apparent since the disease is observed almost exclusively when the mutation is transmitted from the father [6, 15]. A maternal imprinting has therefore been postulated for 11q PGL genes but, despite the pattern of inheritance, *SDHD* shows bi-allelic expression in normal tissues and neural crest derived cancers including lymphoblastoid cell lines from affected and carriers, brain tissue, fetal kidney, PGLs, PHEOs and neuroblastomas [10, 31, 32]. Moreover, *SDHD* promoter methylation has not been found in neuroendocrine tissues and related tumours [32, 33]. Based on the frequent somatic loss of the entire maternal chromosome 11 in *SDHD*-related PGLs, it has been postulated a possible involvement of imprinted genes in other regions of the same chromosome such as those of the Beckwith-Wiedemann (BW) locus on 11p15.5 [34, 35]. Hensen *et al.* hypothesized that, the somatic selective loss of the whole maternal chromosome 11 (targeting both the wild type *SDHD* allele and a maternally-expressed tumour suppressor gene) (TSG) can explain the exclusive paternal transmission of the disease. Indeed, loss of the maternal 11p15 occurs frequently in paediatric tumors including Wilms’ tumours, embryonal rhabdomyosarcoma, hepatoblastoma and adrenocortical carcinoma thus suggesting the involvement of *CNKNIC* (p57^{Kip2}) and/or *H19-IGF2* dysregulation in tumorigenesis [36, 37]. Interestingly, loss of 11p has been demonstrated in 33–50% of HNPGLs, in 27% of abdominal PGLs, in 17–48% of sporadic PHEOs and in 40% to 86% of PHEOs from MEN2A and Von Hippel Lindau (VHL) patients, respectively [38–41]. Moreover, a decreased expression of *CNKNIC* (p57^{Kip2}) and *H19* has been found in PHEOs [42] and the preferential loss of the maternal rather than paternal 11p15.5 has been confirmed in the same tumours [43] thus supporting the hypothesis proposed by Hensen *et al.* Possible evidence supporting the involvement of the BW locus in the parent-of origin effect is given by the work of Pigny and colleagues on a family with an affected child who inherited the *SDHD* mutation p.Trp43X from his mother [44]. The child developed a jugulo-tympanic PGL at 11 years of age and genetic analysis revealed hyper-methylation of two CpGs within the seventh region (CTS7) of binding for the CCCTC-binding factor (CTCF) in the differentially methylated region 1 (DMR1) upstream the *H19* gene. Long-range PCR excluded the presence of genomic deletions in the region. A normal pattern of methylation was shown in the affected mother, the healthy brother who had inherited the *SDHD* germline mutation, and the healthy father. However, no further information was given about the presence of clinical signs related to the BW syndrome in the child affected by the cervical PGL, as expected in case of imprinting changes at DMR1 (i.e. silencing of *H19* - *IGF2* over expression).

***SDH* germline mutations associated with inherited predisposition to neuroendocrine tumours**

For the purpose of this study, 95 papers have been reviewed dealing with *SDH* germline mutations (57 in *SDHD*, 54 in *SDHB* and 13 in *SDHC*) in patients affected by tumours related with the “paranglioma/pheochromocytoma syndromes” [10–12, 31, 33, 35, 44, 45–134]. They include all published reports cited in the LOVD *SDH* gene databases at July 2008 (*SDHB* 080626: June 26, 2008; *SDHC* 080520: May 20, 2008; *SDHD* 080703: July 03, 2008) [135] and 13 recent publications. Data have been collected in a database with the aim to define the mutation spectrum of the three genes and the clinical characteristics of affected carriers.

Two-hundred-twenty-seven index cases carriers of *SDHB* germline mutations have been reported to date, including 216 deleterious mutations and 11 variants (missense and intronic

substitutions) of unknown biological significance (VUS) for a total of 275 affected patients including 48 family members. Germline mutations are scattered along exon 1 to 7 with the fewer mutations identified in exon 5 and no point mutations involving exon 8 (figure 1.1). Twenty-seven percent (58/216) of mutated index cases carry unique mutations while 73% (158/216) have 40 mutations that are recurrent in 2 to 14 independent families. Among the 98 different germline mutations, 46% are missense, 23% frameshift, 13% splicing defect, 9% nonsense, 2% deletion/insertion of one amino acid and 7% are large genomic deletions involving the whole gene [64], exon 2 to 8 [47], exon 6 to 8 [100, 113] or limited to exon 1 [47, 65]. At least two different exon 1 deletions have been described, one of 15.7 kb that was recurrent in Spain and another, 20 kb long, that was found in French families. Despite the presence in *SDHB* intron 1 of eleven Alu repeats covering 36% of the sequence, the mechanism underlining the Spanish deletion seems to be the DNA polymerase α frameshift hot spot GGGGGA at position + 2 while no obvious motif has been recognized that could be responsible for the French deletion [64, 65, 99]. Other recurrent mutations include the splice site IVS2+1G>T (c.72+1G>T) identified in 9 cases of Scottish origin, p.Arg46X identified in 9 families from UK and US, p.Arg242His in 9 families from Germany and Belgium, p.Arg90X and p.Arg46Gln in 9 and 14 different families, respectively, of various ethnical origin.

Two-hundred-ninety-nine index cases have been reported as carriers of *SDHD* germline mutations including 289 deleterious mutations and 10 VUS in a total of 405 affected patients including 106 family members. Germline mutations are scattered along exon 1 to 4 with the exon 3 mutated in 60% of cases (figure 1.2). Fourteen percent (40/289) of mutated index cases carry unique mutations while in 86% (249/289) of cases 28 mutations have been identified, recurrent in 2 to several independent families. Among the 68 different germline mutations reported to date, 40% are frameshift, 25% nonsense, 19% missense (clustered in exon 3 and 4), 9% splicing defect, 4% in-frame deletions of 1 to 4 amino acids and 2% are large genomic deletions involving the whole gene [99] or exon 3 [75]. Well known recurrent mutations with a founder effect include p.Asp92Tyr, p.Leu95Pro and p.Leu139Pro in Dutch patients, p.Gln109X in central Italy and p.Met1Ile in Chinese families while the p.Pro81Leu has been suggested as hot spots for new mutations due to C>T transition.

Only nineteen index cases have been reported to date as carriers of *SDHC* germline mutations with a total of 30 affected patients including 11 family members. Germline mutations are scattered along exon 1 to 6 with a few missense mutations involving exon 4 and 6 (figure 1.3). Sixty-three percent (12/19) of mutated index cases carry unique mutations while 37% (7/19) have 3 recurrent mutations in 2 to 3 independent families. Among the 15 different germline mutations reported to date, 7 (47%) are nonsense, 5 (33%) splicing defect, 2 (19%) missense and one (7%) Alu-mediated genomic deletion of 8.4 kb involving exon 6 [56].

Prevalence of germline mutations in the *SDH* genes

As it will be shown in the next paragraph, germline mutations in *SDH* genes are associated with sporadic and familial PGLs involving either sympathetic paraganglia (mainly abdominal, adrenal or extra-adrenal) or parasympathetic organs in the head and neck region. Despite the parent-of-origin effect of *SDHD* germline mutations, 61% of mutated index cases have a positive family history for PGLs while 69% of *SDHB* mutations carriers have an apparent negative family history. The few *SDHC* mutated cases described to date have a positive family history in 62.5% of the cases. Therefore, the prevalence of *SDHB* germline mutations among sporadic cases (tables 1 and 4) is somewhat higher than that one of *SDHD* (6% versus 3% for PHEOs/PGLs, 6.5% versus 2.4% for HNPGLs).

Very few sporadic cases have been reported with *SDHC* germline mutations (0.6%, table 4). The general prevalence of *SDH* mutations among sporadic and non-syndromic cases of adrenal and extra-adrenal PGLs is around 6% (50/795) with 9% of frequency in cases tested negative for *RET* and *VHL* mutation. However, the prevalence of *SDH* mutations is considerably higher in sporadic extra-adrenal tumours (15/45, 33%), malignant tumours (38%, table 2) and paediatric cases (29%, table 3) with strong preponderance of *SDHB* mutations in all categories. *SDH* mutations seem less frequent than *RET* and *VHL* in bilateral or familial adrenal PHEOs with a prevalence around 10–17% while in familial aggregations of adrenal and extra-adrenal tumours (including HNPGLs) the frequency reaches 85% (11/13) (table 3). Similar *SDH* mutations frequencies can be found in cases affected by HNPGLs outside the area of Low Countries (table 4). The general prevalence of mutations among sporadic, multiple and familial HNPGLs is 9.5%, 71% and 88%, respectively, with a predominance of *SDHD* germline mutations among multiple and familial cases, in accordance to the overall higher penetrance of mutations of this gene. In the Netherlands and Belgium (table 5) due to the presence of founder mutations associated with the low altitude (which decreases the hypoxic stimulation of paraganglia) the prevalence of *SDH* mutations among sporadic cases is remarkably higher (29%) and all familial cases that are not linked to PGL2 are caused by *SDHD* germline mutations.

Clinical manifestations and penetrance of *SDH* germline mutations

Analysis of the clinical manifestations of 689 published carriers of deleterious mutations in *SDHB* (264), *SDHC* (30) and *SDHD* (395) led to the recognition of a genotype-phenotype correlation. Affected carriers of *SDHD* and *SDHC* mutations have more frequently a positive family history (61% and 62.5%, respectively) than *SDHB* mutation carriers (31%). Median age at diagnosis of the first tumour is similar in *SDHB* and *SDHD* mutations carriers (32 and 33 years of age, respectively) and lower than that in *SDHC* mutation carriers (38 years). As shown by the analysis of the mean ages at diagnosis (figure 2, left panels), 25% of affected *SDHB* carriers have been diagnosed in the first and second decades of life while only 15% of *SDHD* mutation carriers and no *SDHC* mutation carriers have been diagnosed in the first decade of life. Multiple primary tumours are frequently observed in *SDHD* mutation carriers (79%, 167/211 with available information) while patients with *SDHB* and *SDHC* mutations have single tumours in 67% and 73% of the cases, respectively. As shown in figure 2 (right panels) the most frequent phenotype associated with *SDHB* germline mutations is the development of extra-adrenal PGL (53%, 140/264), mainly abdominal (including pelvis and retro-peritoneum) but also thoracic, mediastinal and cervical. Twenty percent of cases presents with adrenal PHEO alone or associated with PGL (52/264) and another 20% of cases develops only HNPGL (52/264). On the contrary, *SDHD* affected carriers presented with only HNPGL, single or multiple, in 78% of cases (305/395) while adrenal PHEO and/or extra-adrenal PGL are the sole manifestations in 8% (31/395) and 1% (1/395) of cases. Among the 30 *SDHC* affected carriers reported to date, 87% (26/30) presented with HNPGL alone while PGL and PHEO occurred more rarely. Tables 6, 7 and 8 summarize the clinical manifestations of *SDH* subunit mutation carriers as per published reports and including data included in the present report.

The penetrance of *SDH* germline mutations has been addressed by two major studies [58, 106]. According with data from the “Freiburg-Warsaw registry” [106] *SDHB* mutation carriers have a life time cancer risk of 76% with 50% penetrance by age 35 while *SDHD* carriers who inherited the mutation from their father seem to have a life time cancer risk of 100% with penetrance of 50% by age 31 and 86% by age 50. A penetrance of 50% by age 33 for *SDHD* has been confirmed for a founder mutation in the Italian population [122]. Slightly lower numbers have been reported for *SDHB* germline mutations by the “International *SDH* consortium” [58] with an estimated penetrance of 29% by age 30 years

and 45% by age 40 while for *SDHD* carriers the penetrance was similar to the one previously reported (48% by age 30 years and 73% by age 40). Considering the tumour location, both studies recognized a prevalence of extra-adrenal abdominal paragangliomas in *SDHB* mutation carriers (50% of *SDHB* carriers vs 21% of *SDHD* in Neumann HP *et al.* – 67% of *SDHB* carriers vs 18% of *SDHD* in Benn DE *et al.*) and a prevalence of HNPGLs in *SDHD* mutation carriers (79% of *SDHD* carriers vs 31% of *SDHB* in Neumann HP *et al.* – 89% of *SDHD* carriers vs 27% of *SDHB* in Benn DE *et al.*). Results were conflicting for adrenal PHEOs (53% of *SDHD* carriers vs 28% of *SDHB* in Neumann HP *et al.* – 7% of *SDHD* carriers vs 18% of *SDHB* in Benn DE *et al.*) and slightly different for thoracic PGLs (18% of *SDHD* carriers vs 9% of *SDHB* in Neumann HP *et al.* – 11% of *SDHD* carriers and 18% of *SDHB* in Benn DE *et al.*). In *SDHD* mutation carriers, life at high altitude has been shown to increase the risk of developing multiple primary tumors and PHEOs. An increased risk of PHEOs has also been recognized for truncating mutations [49]. In light of these data, the very low altitude in the Netherlands associated with the presence of recurrent missense mutations can explain the peculiarly high rates of *SDHD* germline mutations among sporadic cases of HNPGL (table 5) and the overall low risk of PHEO among Dutch carries.

Finally, both studies underlined the prevalence of multiple tumours among *SDHD* mutation carriers (74% of *SDHD* carriers vs 28% of *SDHB* carriers in Neumann HP *et al.* – 30% of *SDHD* carriers vs 12% of *SDHB* in Benn DE *et al.*) and the increased risk for malignant tumours in *SDHB* carriers, although with different extent (34% of *SDHB* carriers vs 0% of *SDHD* in Neumann HP *et al.* – 37.5% of *SDHB* carriers vs 8% of *SDHD* in Benn DE *et al.*). Even higher risk for malignancy (defined as the presence of metastases or histologically documented lymph-node invasion) in *SDHB* mutation carriers has been reported by other groups (71.4% by Amar L *et al.*) [46, 127] most likely reflecting differences in clinical evaluation, follow-up, and sources of recruitment between different centres. In malignant tumours the presence of an *SDHB* germline mutation seems to correlate with worse prognosis including a five-year probability of survival of 36% compared to 55% and a median time from presentation to first metastasis of 4 months compared to 20 months in the absence of *SDHB* mutations [47]. However, longer survival and longer disease-free interval have been reported by other authors [60, 123, 127, 132]. In carriers of *SDHD* mutations, development of malignant tumors has been reported occasionally giving a life time risk of malignancy between 2.5% and 7.7% [49, 58, 74, 82–84, 111, 112, 128]. In the present survey, the prevalence of malignant tumours among affected carriers has been determined as 41% (105/256) for *SDHB*, 4% (20/395) for *SDHD* and 3% (1/30) for *SDHC*. In an attempt to define the risk for malignancy for each type of tumour, it is interesting to note that malignant disease has been reported for *SDHB* mutations in 12% of patients affected by HNPGL alone, in 35% of patients with only adrenal PHEO and in 48% of cases with only extra-adrenal PGLs. A similar trend for an increased risk of malignancy related to extra-adrenal PGL is present also in *SDHD* mutation carriers in whom malignant tumours are reported in 4% of patients with HNPGL alone, 6% of cases with only adrenal PHEO and 17% of patients with extra-adrenal PGLs.

Other tumours associated with *SDH* germline mutations

The best known association of *SDH* germline mutations with other tumours is the Carney-Stratakis syndrome (or dyad) of PGLs and gastrointestinal stromal tumours (GIST) [100, 113]. Germline point mutations or large deletions were identified in *SDHB*, *C* and *D* genes in 7 out of 9 index cases with GIST and/or PGLs. Loss of the normal allele was demonstrated in all GIST samples analysed (3 for *SDHB*, 2 for *SDHC* mutations). An additional family with extra-adrenal PGLs and a relative affected by GIST has been reported in association with an *SDHB* missense mutation [59].

The identification of *SDHB* germline mutations (c.713_716delTCTC) in two siblings affected by paraganglioma and clear cell renal carcinoma at 21 and 26 years of age [106] suggested a possible involvement of *SDH* genes in renal tumorigenesis. Indeed both renal tumors showed losses of the normal allele as it was shown for another renal cancer (with apparent mixture of clear cells and cells with granular-eosinophilic cytoplasm) developed at 28 years of age by a carrier of the *SDHB* p.Arg27X germline mutation. The latter patient inherited the mutation from her mother affected by heart PGL at 55 years [129]. However, no additional *SDHB* or *SDHD* mutations have been identified in a cohort of 95 renal cell tumours while a renal angiomyolipoma and a renal oncocytoma were found in two carriers of *SDHB* large deletions [64, 65] and a malignant papillary type II renal cell cancer in a carrier of an *SDHB* nonsense mutation [123]. Recently, screening of 68 patients affected by familial or multiple/early-onset renal cell cancer for germline *SDH* mutations led to the identification of 3 additional carriers of *SDHB* mutations (p.Arg11His, p.Arg46X, p.Arg46Gln) [119] thus confirming a possible increased risk for RCC limited to carriers of *SDHB* germline mutations. A unique case of testicular seminoma has been reported among carriers of *SDHD* mutations (p.Trp43X); the causative role of the germline mutation is suggested by the loss of the normal allele in this tumour [77]. Interestingly, both RCC and testicular tumours have been reported in carriers of *FH* germline mutations, another gene with tumor suppressor function encoded by a mitochondrial enzyme (fumarate hydratase or fumarase). The prevalent manifestations of *FH* mutations are cutaneous and uterine leiomyomas, RCC (mainly papillary type II); testicular (Leydig cell tumours) and adrenocortical tumors can also occur [136–138].

Finally, it has been suggested that germline *SDHD* mutations could be responsible for hyperplasia of thyroid C-cells secreting calcitonin. However, the mutation identified in a family with four members affected by hypercalcitoninemia (p.His50Arg) is indeed a common polymorphism [63, 139]. Germline *SDHB* and *SDHD* variants have been identified in 10 patient out of 74 (13.5%) affected by Cowden-like clinical manifestations (breast, thyroid, uterine benign and malignant diseases) [108]; although some of these sequence changes are considered polymorphisms (*SDHB* p.Ser163Pro, *SDHD* p.Gly12Ser and p.His50Arg), they appear to function as low penetrance alleles.

It remains unclear if *SDH* mutations can be associated with other tumours that are occasionally found in affected carriers or their relatives such as papillary thyroid cancers [106, 127], adrenal neuroblastoma [65], pituitary adenoma [58, 93], bronchial carcinoid [94], ependymoma, melanoma, bone and soft tissue sarcoma [49], B-cell lymphoma [111] and colon cancer [58, 99].

Somatic second hits associated with *SDH* germline mutation

Germline loss of function mutations associated with frequent somatic deletions of the wild type (wt) allele suggest that *SDH* genes behave as classical tumour suppressor genes (TSG) as they need two events for inactivation. PGLs and PHEOs are tumours composed by cancer cells, normal sustentacular cells and a variable amount of small vessels. In light of this particular histology (characterized by an intrinsic relatively large component of normal cells), the classical approach to search for somatic deletion of the wt allele through loss-of-heterozygosity (LOH) (i.e. microsatellite analysis or sequencing of the mutated exon) on whole tumour DNA can fail to detect the second hit while loss of the wt allele is unequivocally shown on aneuploid tumour fraction [126], microdissected tumours cells [122] or tumour RNA [31]. However, even by simple LOH analysis or allelic-imbalance, somatic deletion of the wt allele is present in at least 78.5% of *SDHD*-related tumours (33/45 HNPGLs and 11/11 adrenal or extra-adrenal PHEOs [10, 31, 34, 35, 51, 70, 81, 122, 126, 130], 60% of *SDHB*-related tumours (15/25 adrenal or extra-adrenal PHEOs) [12, 66, 79, 80, 85, 95, 113, 129, 132] and in all 5 tumours studied from carriers of *SDHC* germline

mutations [11, 56, 93, 113]. No somatic point mutations or promoter hyper-methylation have been reported to date as a possible “second hit”. The somatic deletion of the wt *SDH* allele seems therefore the preferential second hit and this observation can suggest the need of concomitant loss of neighbouring TSG/s. Indeed, *SDHD* germline mutations seem invariably associated with somatic loss of the entire chromosome 11 implying the concomitant loss of maternally-expressed TSGs on 11p15.5 [34] and perhaps other TSGs on the long and the short arms of the same chromosome. Loss of the whole maternal chromosome 11 would therefore provide with a single event a great growth advantage thus explaining the almost complete penetrance of *SDHD* germline mutations upon paternal transmission. Interestingly, somatic gains of genomic material of 11cen-q13 (i.e. the opposite somatic alteration) have been shown in 36% of extra-adrenal PHEOs and in 25% of malignant PGLs [40] which are relatively infrequent clinical manifestations in *SDHD* mutation carriers. An association between 11q13 gain and malignant PHEOs and PGLs has been confirmed also in another study [39]. In the case of *SDHB* germline mutations, deletions of the short arm of chromosome 1 can be associated with the concomitant loss of TSGs located in 1p36.2–1p36.3 (the neuroblastoma-TSG region) or even more centromeric such as 1cen-p31 and 1p32.1–1p32.3 (the PHEOs-TSG regions) [41, 140, 141].

The “chromosomal-site-effect” could explain the rarity and the absence of germline mutations in *SDHC* and *SDHA*, respectively, in the paraganglioma-pheochromocytoma syndrome. If no relevant TSGs are located in neighbouring regions of 1q and 5p, multiple somatic events will be required to achieve a substantial growth advantage, an occurrence statistically rare or even impossible in slow growing cells such as those derived from neural crest. In adrenal or extra-adrenal PHEOs loss or gain of genomic material on chromosome 1q or 5p are very rare events: the few aberrations reported (in malignant tumours mainly) included whole chromosome 1 monosomy or chromosome 5 trisomy [40, 41, 140]. A comparative genomic hybridisation (CGH) study, comparing somatic aberrations between PHEOs and HNPGLs, underlined the presence of 1q losses only in HNPGLs [39]. Another study on HNPGLs failed to detect any 1q loss at CGH while there were two 5p deletion among the 16 tumours analysed (12.5%); in just one case the region lost included the *SDHA* gene (whole short arm deletion) and curiously this chromosomal aberration was associated with loss of 11p [38]. A more precise characterization of the somatic alterations associated with *SDHB* and *SDHC* germline mutations will improve our knowledge on the mechanisms underlining tumourigenesis.

Biological effect of *SDH* germline mutation

Gimenez-Roqueplo and colleagues [78] first studied the biological effect of a loss of function *SDHD* germline mutation (p.Arg22X): a complete loss of the maternal wt allele was found in the related extra-adrenal PGL of the mediastinum where both functions of SDH were completely abolished, i.e. the catalytic activity of succinate dehydrogenase and the electron flow to the ubiquinone pool. Six sporadic PHEOs analysed as controls showed normal SDH activity. The same tumour and three carotid body PGLs from the same family showed high expression of hypoxia inducible factors (HIF) 1 α , 2 α and vascular endothelial growth factor (VEGF) while large vessels strongly expressed VEGF-receptor 1 and VEGF-R2. These results strongly suggested the activation of the hypoxia/angiogenesis pathway as possible mechanism underlying tumour development. The same group [79] studied the biological effect of a missense *SDHB* germline mutation (p.Arg46Gln) in a malignant PHEO with somatic terminal deletion of 1p. Again, in tumour tissue the succinate dehydrogenase activity was abolished with increased expression of HIF2 α and VEGF in tumour cells associated with increased expression of VEGF-R1 and VEGF-R2 in vascular endothelial in agreement with the high vascularization of this endocrine tumour. Moreover, a complete and selective loss of mitochondrial complex II enzymatic activity was confirmed in additional 7

tumours (extra-adrenal and/or malignant PHEOs) from carriers of *SDHB* germline mutations (frame-shift and missense) with somatic loss of 1pter–1p34.3 [80]. Even in non-malignant tumours, the presence of an *SDHB* germline mutation was associated with changes in vascular morphology (arcs, networks and parallel structures). Similar findings have been reported by Douwes Dekker PB *et al.* [71] who studied the SDH enzymatic activity in 22 HNPGLs from Dutch patients, 12 from carriers of *SDHD* and *SDHB* germline mutations, 2 from the PGL2 linked family and 8 sporadic. In all hereditary HNPGLs, including those related to PGL2, the SDH enzymatic activity was absent (78.6%) or very weak (21.4%) with over-expression of the SDHA subunit which showed diffuse cytoplasmic expression at immunohistochemistry. Moreover, two *SDHD*-related PGLs analysed by electron microscopy showed increased number of mitochondria in tumour cells with swollen appearance, loss of cristae and inclusion bodies. Interestingly, unlike sporadic PHEOs, most of sporadic HNPGLs (75%) were negative for SDH enzymatic activity as well, thus suggesting that impairment of mitochondrial complex II could be a common feature in the tumorigenesis of chemoreceptor PGLs. However, no somatic point mutations have been identified in SDH genes in a number of sporadic tumours (HNPGLs) [51, 69, 101]. Finally, a severe decrease in SDH activity was demonstrated also for a germline *SDHC* mutations in a sample of GIST tumour with loss of the wt allele [100]. These data support the notion that, whenever an *SDH* subunit gene is mutated, SDH enzymatic activity is strongly compromised. To further investigate the metabolic consequences of SDH deficiency, Pollard and colleagues analysed frozen PGLs from carriers of two *SDHB* missense mutations (p.Ser100Pro and p.Ile127Ser) with somatic loss of the entire wt 1p or whole 1 chromosome. Compared to sporadic tumours, SDH deficient PGLs showed gross accumulation of succinate, positive succinate to fumarate ratio and increased expression of HIF1 α and VEGF with high density of micro-vessels [142]. *In vitro* inactivation of SDH activity and succinate accumulation was shown to inhibit prolyl-hydroxylation of HIF1 α and HIF2 α which is an essential step for its degradation through the complex VHL-ElonginD-C-Cul2 [143]. In fact, prolyl-hydroxylases (PHD1, 2 and 3, also known as EglN2, 1 and 3, respectively) couple their enzymatic activity with oxidation and decarboxylation of α -ketoglutarate to succinate with PHD2 (EglN1) playing the major role in HIF α downregulation. SDH deficiency finally mimics the hypoxic condition with increased activity of Hypoxia Inducible Factors able to trigger changes in cellular metabolism, angiogenesis, cell scattering and cell proliferation [144]. Consistent with the hypothesis implicating HIF dysregulation in the pathogenesis of *SDH* related tumours, gene expression micro-arrays studies have confirmed over-expression of hypoxia-induced angiogenic pathway genes in both *SDHB* and *SDHD* related PHEOs with coordinated suppression of oxidoreductase (i.e. mitochondrial function), a profile similar to neuroendocrine tumours from VHL patients [68]. Finally, prolyl-hydroxylase 3 (EglN3 or PHD3) has been shown to mediate c-Jun developmental apoptosis in sympathetic neurons when levels of nerve growth factor become a limiting condition for neuronal survival. Thus, inhibition of EglN3-PHD3 consequent to succinate accumulation can promote cell survival and proliferation also through a HIF-independent pathway [145].

Somatic *SDH* mutations in sporadic tumours

Somatic point mutations in *SDH* genes seem very rare. To date, only a few somatic mutations have been identified in PHEO and PGL specimens. In a cohort of more than 480 tumour sample analysed (139 HNPGLs, 321 adrenal/extra-adrenal PHEO, 22 PGLs of the cauda equina, table 9) [12, 33, 50, 51, 69, 70, 80, 81, 85, 101, 146–151], just two *SDHB* (p.Arg217Cys in a carotid body pgl [147], p.Ser100Phe in an extra-adrenal PGL [84, 152]) and three *SDHD* (p.81Leu in a sporadic PHEO [81], p.Met1Val in a sporadic HNPGL [35] and p.Tyr114Cys in a jugular PGL [147]) somatic mutations have been reported, all associated with LOH of the wt allele. In the same tumours, heterozygote somatic deletions (LOH) seem more frequent involving the *SDHB* locus on 1p36 in 35–58% of PHEO/PGLs

and the *SDHD* locus on 11q23 in 17–69% of the same tumours (table 9) but their causative role is still unclear giving the lack of information about the functional state of the remaining allele and of complex II enzymatic activity. The short arm of chromosome 1 and the long arm of chromosome 11 are among the chromosomal regions more frequently lost in sporadic and hereditary neuroendocrine tumours and probably they harbour other relevant TSGs.

Silencing of *SDH* genes through promoter methylation has been addressed in a few studies but never demonstrated until now (analysis of 35 PHEOs for all three *SDH* genes in Cascón A *et al.* [33], analysis of 81 neuroblastomas for *SDHD* in De Preter K *et al.* [32], analysis of 28 PHEOs and 46 neuroblastomas for *SDHB* in Astuti D *et al.* [153]). However, somatic deletion of *SDHD* in those tumours characterized by LOH at 11q23 (table 10) (group 2B neuroblastomas, midgut carcinoids, neuroendocrine tumours, PHEOs from carriers of VHL missense mutations) [32, 129, 149, 150, 153–157] could suggest a role in tumorigenesis through a mechanism of haploinsufficiency, supported by the consistent reduction of transcript levels found in some tumours [32, 41, 150]. A marked reduction of *SDHB* expression has been found in VHL-related PHEOs which are characterized by frequent loss of 1p as well [68] and the *SDHB* haploinsufficiency can be responsible for the activation of the hypoxia-angiogenesis pathway even in those tumours with VHL type 2c mutations which seems unable to interfere with HIF degradation. Moreover, HIF1 α seems to be able to down-regulated *SDHB* expression thus suppressing the function of mitochondrial complex II in an auto-regulatory loop [68].

Concluding remarks

PGLs and PHEOs are mostly benign tumours although they can result in significant clinical morbidity related to the mass effect, cranial nerve palsies or the secretion of catecholamines. If left untreated, these tumours can also metastasise and a malignant potential has been specifically recognized for *SDHB* related adrenal and extra-adrenal PHEOs. Early treatment of these tumours can result in a significant decrease in morbidity and mortality through the identification of at risk individuals that need proper surveillance and treatment. A reasonable minimum monitoring program should start in the second decade of life and include a careful history and physical examination, annual measurement of the blood pressure and urinary catecholamines (epinephrine, norepinephrine, dopamine and vanillylmandelic acid) in addition to bi-annual imaging by CT scan and/or magnetic resonance of the neck and skull base, thorax, abdomen and pelvis. An additional screening method, positron emission tomography with [^{18}F]fluorodopa or [^{18}F]fluorodopamine or ^{123}I iodine metaiodobenzylguanidine (MIBGE) scintigraphy may be employed as needed [58, 158]. Giving the bi-allelic expression of *SDHD*, that argues against its maternal imprinting, and the complete loss of SDH enzymatic activity whenever one of its subunits is mutated, a possible explanation of the phenotypic variability in paraganglioma-pheochromocytoma syndrome can be the size and location of the somatic deletions of the normal allele which may compromise the function of other TSGs located nearby in the form of cis or even trans effects.

Acknowledgments

The work of BP has been supported by Compagnia di San Paolo (Progetto Oncologia), AIRC (Italian Association on Cancer Research), Ricerca finalizzata Regione Piemonte. Authors are grateful to Barbara Ferrando for helping in data management. Also, this work was supported in part by NIH intramural project Z01-HD-000642-04 and by a Bench-to-Bedside Award from the Office of Rare Disorders (ORD) and the National Institute of Child Health & Human Development (NICHD), NIH, for the study of the “Genetics of inherited paragangliomas and gastric stromal tumors associated with adrenal and other tumors” both to Dr. C.A. Stratakis

Abbreviations

BW	Beckwith-Wiedemann
CGH	comparative genomic hybridization
GIST	gastro-intestinal stromal tumours
HIF	hypoxia inducible factor
HNPGL	head and neck paraganglioma
MEN2A	multiple endocrine neoplasia type 2A
PGL	paraganglioma
PHEO	pheochromocytoma
RCC	renal cell cancer
ROS	reactive oxygen species
SDH	succinate dehydrogenase
TSG	tumour suppressor gene
VEGF	vascular endothelial growth factor
VHL	von Hippel Lindau
VUS	variant of unknown biological significance
WT	wild type

References

1. Heutink P, van der Mey AG, Sandkuijl LA, et al. A gene subject to genomic imprinting and responsible for hereditary paragangliomas maps to chromosome 11q23-qter. *Hum Mol Genet.* 1992; 1:7–10. [PubMed: 1301144]
2. Heutink P, van Schothorst EM, van der Mey, et al. Further localization of the gene for hereditary paragangliomas and evidence for linkage in unrelated families. *Eur J Hum Genet.* 1994; 2:148–158. [PubMed: 7834274]
3. Baysal BE, Farr JE, Rubinstein WS, et al. Fine mapping of an imprinted gene for familial nonchromaffin paragangliomas, on chromosome 11q23. *Am J Hum Genet.* 1997; 60:121–132. [PubMed: 8981955]
4. Milunsky J, DeStefano AL, Huang XL, et al. Familial paragangliomas: linkage to chromosome 11q23 and clinical implications. *Am J Med Genet.* 1997; 72:66–70. [PubMed: 9295078]
5. Mariman EC, van Beersum SE, Cremers CW, van Baars FM, Ropers HH. Analysis of a second family with hereditary non-chromaffin paragangliomas locates the underlying gene at the proximal region of chromosome 11q. *Hum Genet.* 1993; 91:357–361. [PubMed: 8388849]
6. Mariman EC, van Beersum SE, Cremers CW, Struycken PM, Ropers HH. Fine mapping of a putatively imprinted gene for familial non-chromaffin paragangliomas to chromosome 11q13.1: evidence for genetic heterogeneity. *Hum Genet.* 1995; 95:56–62. [PubMed: 7814027]
7. Niemann S, Steinberger D, Müller U. PGL3, a third, not maternally imprinted locus in autosomal dominant paraganglioma. *Neurogenetics.* 1999; 2:167–170. [PubMed: 10541590]
8. Niemann S, Becker-Follmann J, Nürnberg G, et al. Assignment of PGL3 to chromosome 1 (q21–q23) in a family with autosomal dominant non-chromaffin paraganglioma. *Am J Med Genet.* 2001; 98:32–36. [PubMed: 11426453]
9. Sato T, Saito H, Yoshinaga K, Shibota Y, Sasano N. Concurrence of carotid body tumor and pheochromocytoma. *Cancer.* 1974; 34:1787–1795. [PubMed: 4371947]
10. Baysal BE, Ferrell RE, Willett-Brozick JE, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science.* 2000; 287:848–851. [PubMed: 10657297]

11. Niemann S, Müller U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nat Genet.* 2000; 26:268–270. [PubMed: 11062460]
12. Astuti D, Latif F, Dallol A, et al. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *Am J Hum Genet.* 2001; 69:49–54. [PubMed: 11404820]
13. Parry DM, Li FP, Strong LC, Carney JA, Schottenfeld D, Reimer RR, Grufferman S. Carotid body tumors in humans: genetics and epidemiology. *J Natl Cancer Inst.* 1982; 68:573–578. [PubMed: 6951072]
14. Grufferman S, Gillman MW, Pasternak LR, Peterson CL, Young WG Jr. Familial carotid body tumors: case report and epidemiologic review. *Cancer.* 1980; 46:2116–2122. [PubMed: 7000334]
15. van der Mey AG, Maaswinkel-Mooy PD, Cornelisse CJ, Schmidt PH, van de Kamp JJ. Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. *Lancet.* 1989; 2:1291–1294. [PubMed: 2574254]
16. Sobol SM, Dailey JC. Familial multiple cervical paragangliomas: report of a kindred and review of the literature. *Otolaryngol Head Neck Surg.* 1990; 102:382–390. [PubMed: 2113266]
17. Drovdic CM, Myers EN, Peters JA, Baysal BE, Brackmann DE, Slaterry WH 3rd, Rubinstein WS. Proportion of heritable paraganglioma cases and associated clinical characteristics. *Laryngoscope.* 2001; 111:1822–1872. [PubMed: 11801952]
18. Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Plouin PF. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. *J Clin Endocrinol Metab.* 2005; 90:2110–2116. [PubMed: 15644401]
19. Khorram-Manesh A, Ahlman H, Nilsson O, et al. Long-term outcome of a large series of patients surgically treated for pheochromocytoma. *J Intern Med.* 2005; 258:55–66. [PubMed: 15953133]
20. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, et al. Clinical experience over 48 years with pheochromocytoma. *Ann Surg.* 1999; 229:755–764. [PubMed: 10363888]
21. Maher ER, Eng C. The pressure rises: update on the genetics of pheochromocytoma. *Hum Mol Genet.* 2002; 11:2347–2354. [PubMed: 12351569]
22. Bausch B, Borozdin W, Mautner VF, et al. European-American Pheochromocytoma Registry Study Group. Germline NF1 mutational spectra and loss-of-heterozygosity analyses in patients with pheochromocytoma and neurofibromatosis type 1. *J Clin Endocrinol Metab.* 2007; 92:2784–2792. [PubMed: 17426081]
23. Schlisi S, Kenchappa RS, Vredevelde LC, et al. The kinesin KIF1Bbeta acts downstream from EglN3 to induce apoptosis and is a potential 1p36 tumor suppressor. *Genes Dev.* 2008; 22:884–893. [PubMed: 18334619]
24. Yeh IT, Lenci RE, Qin Y, et al. A germline mutation of the KIF1B beta gene on 1p36 in a family with neural and nonneural tumors. *Hum Genet.* 2008; 124:279–285. [PubMed: 18726616]
25. Dahia PL, Hao K, Rogus J, et al. Familial Pheochromocytoma Consortium. Novel pheochromocytoma susceptibility loci identified by integrative genomics. *Cancer Res.* 2005; 65:9651–9658. [PubMed: 16266984]
26. Cecchini G, Schröder I, Gunsalus RP, Maklashina E. Succinate dehydrogenase and fumarate reductase from *Escherichia coli*. *Biochim Biophys Acta.* 2002; 1553:140–157. [PubMed: 11803023]
27. Yankovskaya V, Horsefield R, Törnroth S, et al. Architecture of succinate dehydrogenase and reactive oxygen species generation. *Science.* 2003; 299:700–704. [PubMed: 12560550]
28. Bourgeron T, Rustin P, Chretien D, et al. Mutation of a nuclear succinate dehydrogenase gene results in mitochondrial respiratory chain deficiency. *Nat Genet.* 1995; 11:144–149. [PubMed: 7550341]
29. Ackrell BA. Progress in understanding structure-function relationships in respiratory chain complex II. *FEBS Lett.* 2000; 466:1–5. [PubMed: 10648801]
30. Ackrell BA. Cytopathies involving mitochondrial complex II. *Mol Aspects Med.* 2002; 23:369–384. [PubMed: 12231007]
31. Badenhop RF, Cherian S, Lord RS, Baysal BE, Taschner PE, Schofield PR. Novel mutations in the SDHD gene in pedigrees with familial carotid body paraganglioma and sensorineural hearing loss. *Genes Chromosomes Cancer.* 2001; 31:255–263. [PubMed: 11391796]

32. De Preter K, Vandesompele J, Hoebeeck J, et al. No evidence for involvement of SDHD in neuroblastoma pathogenesis. *BMC Cancer*. 2004; 4:55. [PubMed: 15331017]
33. Cascon A, Ruiz-Llorente S, Fraga MF, et al. Genetic and epigenetic profile of sporadic pheochromocytomas. *J Med Genet*. 2004; 41:e30. [PubMed: 14985401]
34. Hensen EF, Jordanova ES, van Minderhout IJ, et al. Somatic loss of maternal chromosome 11 causes parent-of-origin-dependent inheritance in SDHD-linked paraganglioma and pheochromocytoma families. *Oncogene*. 2004; 23:4076–4083. [PubMed: 15064708]
35. Riemann K, Sotlar K, Kupka S, et al. Chromosome 11 monosomy in conjunction with a mutated SDHD initiation codon in nonfamilial paraganglioma cases. *Cancer Genet Cytogenet*. 2004; 150:128–135. [PubMed: 15066320]
36. Gicquel C, Raffin-Sanson ML, Gaston V, et al. Structural and functional abnormalities at 11p15 are associated with the malignant phenotype in sporadic adrenocortical tumors: study on a series of 82 tumors. *J Clin Endocrinol Metab*. 1997; 82:2559–2565. [PubMed: 9253334]
37. Tycko B. Epigenetic gene silencing in cancer. *J Clin Invest*. 2000; 105:401–407. [PubMed: 10683367]
38. Dannenberg H, de Krijger RR, Zhao J, et al. Differential loss of chromosome 11q in familial and sporadic parasympathetic paragangliomas detected by comparative genomic hybridization. *Am J Pathol*. 2001; 158:1937–1942. [PubMed: 11395368]
39. Cascón A, Ruiz-Llorente S, Rodríguez-Perales S, et al. A novel candidate region linked to development of both pheochromocytoma and head/neck paraganglioma. *Genes Chromosomes Cancer*. 2005; 42:260–268. [PubMed: 15609347]
40. Edström E, Mahlamäki E, Nord B, et al. Comparative genomic hybridization reveals frequent losses of chromosomes 1p and 3q in pheochromocytomas and abdominal paragangliomas, suggesting a common genetic etiology. *Am J Pathol*. 2000; 156:651–659. [PubMed: 10666394]
41. Lui WO, Chen J, Gläsker S, et al. Selective loss of chromosome 11 in pheochromocytomas associated with the VHL syndrome. *Oncogene*. 2002; 21:1117–1122. [PubMed: 11850829]
42. Liu J, Kahri AI, Heikkilä P, Voutilainen R. Ribonucleic acid expression of the clustered imprinted genes, p57KIP2, insulin-like growth factor II, and H19, in adrenal tumors and cultured adrenal cells. *J Clin Endocrinol Metab*. 1997; 82:1766–1771. [PubMed: 9177379]
43. Margetts CD, Astuti D, Gentle DC, et al. Epigenetic analysis of HIC1, CASP8, FLIP, TSP1, DCR1, DCR2, DR4, DR5, KvDMR1, H19 and preferential 11p15.5 maternal-allele loss in von Hippel-Lindau and sporadic pheochromocytomas. *Endocr Relat Cancer*. 2005; 12:161–172. [PubMed: 15788647]
44. Pigny P, Vincent A, Cardot Bauters C, et al. Paraganglioma after maternal transmission of succinate dehydrogenase gene mutation. *J Clin Endocrinol Metab*. 2008; 93:1609–1615. [PubMed: 18211978]
45. Allibhai Z, Rodrigues G, Brecevic E, Neumann HP, Winquist E. Malignant pheochromocytoma associated with germline mutation of the SDHB gene. *J Urol*. 2004; 172:1409–1410. [PubMed: 15371856]
46. Amar L, Bertherat J, Baudin E, et al. Genetic testing in pheochromocytoma or functional paraganglioma. *J Clin Oncol*. 2005; 23:8812–8818. [PubMed: 16314641]
47. Amar L, Baudin E, Burnichon N, et al. Succinate dehydrogenase B gene mutations predict survival in patients with malignant pheochromocytomas or paragangliomas. *J Clin Endocrinol Metab*. 2007; 92:3822–3828. [PubMed: 17652212]
48. Antonello M, Piazza M, Menegolo M, Opocher G, Deriu GP, Grego F. Role of the genetic study in the management of carotid body tumor in paraganglioma syndrome. *Eur J Vasc Endovasc Surg*. 2008; 36:517–519. [PubMed: 18692411]
49. Astrom K, Cohen JE, Willett-Brozick JE, Aston CE, Baysal BE. Altitude is a phenotypic modifier in hereditary paraganglioma type 1: evidence for an oxygen-sensing defect. *Hum Genet*. 2003; 113:228–237. [PubMed: 12811540]
50. Astuti D, Douglas F, Lennard TW, et al. Germline SDHD mutation in familial pheochromocytoma. *Lancet*. 2001; 357:1181–1182. [PubMed: 11323050]

51. Astuti D, Hart-Holden N, Latif F, et al. Genetic analysis of mitochondrial complex II subunits SDHD, SDHB and SDHC in paraganglioma and pheochromocytoma susceptibility. *Clin Endocrinol (Oxf)*. 2003; 59:728–733. [PubMed: 14974914]
52. Badenhop RF, Jansen JC, Fagan PA, Lord RS, Wang ZG, Foster WJ, Schofield PR. The prevalence of SDHB, SDHC, and SDHD mutations in patients with head and neck paraganglioma and association of mutations with clinical features. *J Med Genet*. 2004; 41:e99. [PubMed: 15235042]
53. Bauters C, Vantyghem MC, Leteurtre E, et al. Hereditary pheochromocytomas and paragangliomas: a study of five susceptibility genes. *J Med Genet*. 2003; 40:e75. [PubMed: 12807974]
54. Bayley JP, van Minderhout I, Weiss MM, et al. Mutation analysis of SDHB and SDHC: novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma. *BMC Med Genet*. 2006; 7:1. [PubMed: 16405730]
55. Baysal BE, Willett-Brozick JE, Lawrence EC, et al. Prevalence of SDHB, SDHC, and SDHD germline mutations in clinic patients with head and neck paragangliomas. *J Med Genet*. 2002; 39:178–183. [PubMed: 11897817]
56. Baysal BE, Willett-Brozick JE, Filho PA, Lawrence EC, Myers EN, Ferrell RE. An Alu-mediated partial SDHC deletion causes familial and sporadic paraganglioma. *J Med Genet*. 2004; 41:703–709. [PubMed: 15342702]
57. Benn DE, Croxson MS, Tucker K, et al. Novel succinate dehydrogenase subunit B (SDHB) mutations in familial pheochromocytomas and paragangliomas, but an absence of somatic SDHB mutations in sporadic pheochromocytomas. *Oncogene*. 2003; 22:1358–1364. [PubMed: 12618761]
58. Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *J Clin Endocrinol Metab*. 2006; 91:827–836. [PubMed: 16317055]
59. Bolland M, Benn D, Croxson M, McCall J, Shaw JF, Baillie T, Robinson B. Gastrointestinal stromal tumour in succinate dehydrogenase subunit B mutation-associated familial pheochromocytoma/paraganglioma. *ANZ J Surg*. 2006; 76:763–764. [PubMed: 16916404]
60. Brouwers FM, Eisenhofer G, Tao JJ, Kant JA, Adams KT, Linehan WM, Pacak K. High frequency of SDHB germline mutations in patients with malignant catecholamine-producing paragangliomas: implications for genetic testing. *J Clin Endocrinol Metab*. 2006; 91:4505–4509. [PubMed: 16912137]
61. Cascón A, Cebrián A, Ruiz-Llorente S, Tellería D, Benítez J, Robledo M. SDHB mutation analysis in familial and sporadic pheochromocytoma identifies a novel mutation. *J Med Genet*. 2002; 39:E64. [PubMed: 12362046]
62. Cascón A, Ruiz-Llorente S, Cebrian A, et al. Identification of novel SDHD mutations in patients with pheochromocytoma and/or paraganglioma. *Eur J Hum Genet*. 2002; 10:457–461. [PubMed: 12111639]
63. Cascón A, Cebrian A, Pollan M, et al. Succinate dehydrogenase D variants do not constitute a risk factor for developing C cell hyperplasia or sporadic medullary thyroid carcinoma. *J Clin Endocrinol Metab*. 2005; 90:2127–2130. [PubMed: 15623805]
64. Cascón A, Montero-Conde C, Ruiz-Llorente S, et al. Gross SDHB deletions in patients with paraganglioma detected by multiplex PCR: a possible hot spot? *Genes Chromosomes Cancer*. 2006; 45:213–219. [PubMed: 16258955]
65. Cascón A, Landa I, López-Jiménez E, et al. Molecular characterisation of a common SDHB deletion in paraganglioma patients. *J Med Genet*. 2008; 45:233–238. [PubMed: 18057081]
66. Castellano M, Mori L, Giacchè M, et al. Genetic mutation screening in an Italian cohort of nonsyndromic pheochromocytoma/paraganglioma patients. *Ann N Y Acad Sci*. 2006; 1073:156–165. [PubMed: 17102082]
67. Cremers CW, De Mönnink JP, Arts N, Joosten FB, Kremer H, Hoefsloot L. Clinical report on the L95P mutation in a Dutch family with paraganglioma. *Otol Neurotol*. 2002; 23:755–759. [PubMed: 12218630]

68. Dahia PL, Ross KN, Wright ME, et al. A HIF1alpha regulatory loop links hypoxia and mitochondrial signals in pheochromocytomas. *PLoS Genet.* 2005; 1:72–80. [PubMed: 16103922]
69. Dannenberg H, Dinjens WN, Abbou, et al. Frequent germ-line succinate dehydrogenase subunit D gene mutations in patients with apparently sporadic parasympathetic paraganglioma. *Clin Cancer Res.* 2002; 8:2061–2066. [PubMed: 12114404]
70. Dannenberg H, van Nederveen FH, Abbou M, Verhofstad AA, Komminoth P, de Krijger RR, Dinjens WN. Clinical characteristics of pheochromocytoma patients with germline mutations in SDHD. *J Clin Oncol.* 2005; 23:1894–1901. [PubMed: 15774781]
71. Douwes Dekker PB, Hogendoorn PC, et al. SDHD mutations in head and neck paragangliomas result in destabilization of complex II in the mitochondrial respiratory chain with loss of enzymatic activity and abnormal mitochondrial morphology. *J Pathol.* 2003; 201:480–486. [PubMed: 14595761]
72. Drucker AM, Houlden RL. A case of familial paraganglioma syndrome type 4 caused by a mutation in the SDHB gene. *Nat Clin Pract Endocrinol Metab.* 2006; 2:702–706. [PubMed: 17143317]
73. Elston MS, Benn D, Robinson BG, Conaglen JV. An apparently sporadic paraganglioma with an SDHB gene germline mutation presenting at age 68 years. *Intern Med J.* 2006; 36:129–131. [PubMed: 16472267]
74. Fakhry N, Niccoli-Sire P, Barlier-Seti A, Giorgi R, Giovanni A, Zanaret M. Cervical paragangliomas: is SDH genetic analysis systematically required? *Eur Arch Otorhinolaryngol.* 2008; 265:557–563. [PubMed: 17987308]
75. Fish JH, Klein-Weigel P, Biebl M, Janecke A, Tauscher T, Fraedrich G. Systematic screening and treatment evaluation of hereditary neck paragangliomas. *Head Neck.* 2007; 29:864–873. [PubMed: 17563904]
76. Fuentes C, Menéndez E, Pineda J, et al. The malignant potential of a succinate dehydrogenase subunit B germline mutation. *J Endocrinol Invest.* 2006; 29:350–352. [PubMed: 16699302]
77. Galera-Ruiz H, Gonzalez-Campora R, Rey-Barrera M, et al. W43X SDHD mutation in sporadic head and neck paraganglioma. *Anal Quant Cytol Histol.* 2008; 30:119–123. [PubMed: 18561749]
78. Gimenez-Roqueplo AP, Favier J, Rustin P, et al. The R22X mutation of the SDHD gene in hereditary paraganglioma abolishes the enzymatic activity of complex II in the mitochondrial respiratory chain and activates the hypoxia pathway. *Am J Hum Genet.* 2001; 69:1186–1197. [PubMed: 11605159]
79. Gimenez-Roqueplo AP, Favier J, Rustin P, et al. Functional consequences of a SDHB gene mutation in an apparently sporadic pheochromocytoma. *J Clin Endocrinol Metab.* 2002; 87:4771–4774. [PubMed: 12364472]
80. Gimenez-Roqueplo AP, Favier J, Rustin P, et al. COMETE Network. Mutations in the SDHB gene are associated with extra-adrenal and/or malignant pheochromocytomas. *Cancer Res.* 2003; 63:5615–5621. [PubMed: 14500403]
81. Gimm O, Armanios M, Dziema H, Neumann HP, Eng C. Somatic and occult germ-line mutations in SDHD, a mitochondrial complex II gene, in nonfamilial pheochromocytoma. *Cancer Res.* 2000; 60:6822–6825. [PubMed: 11156372]
82. Havekes B, Corssmit EP, Jansen JC, van der Mey AG, Vriends AH, Romijn JA. Malignant paragangliomas associated with mutations in the succinate dehydrogenase D gene. *J Clin Endocrinol Metab.* 2007; 92:1245–1248. [PubMed: 17227803]
83. Klein RD, Jin L, Rumilla K, Young WF Jr, Lloyd RV. Germline SDHB mutations are common in patients with apparently sporadic sympathetic paragangliomas. *Diagn Mol Pathol.* 2008; 17:94–100. [PubMed: 18382370]
84. Korpershoek E, Van Nederveen FH, Dannenberg H, et al. Genetic analyses of apparently sporadic pheochromocytomas: the Rotterdam experience. *Ann N Y Acad Sci.* 2006; 1073:138–148. [PubMed: 17102080]
85. Korpershoek E, Petri BJ, van Nederveen FH, et al. Candidate gene mutation analysis in bilateral adrenal pheochromocytoma and sympathetic paraganglioma. *Endocr Relat Cancer.* 2007; 14:453–462. [PubMed: 17639058]

86. Isobe K, Minowada S, Tatsuno I, et al. Novel germline mutations in the SDHB and SDHD genes in Japanese pheochromocytomas. *Horm Res.* 2007; 68:68–71. [PubMed: 17308434]
87. Jeffery J, Devendra D, Farrugia J, et al. Increased urinary dopamine excretion in association with bilateral carotid body tumours: clinical, biochemical and genetic findings. *Ann Clin Biochem.* 2006; 43:156–160. [PubMed: 16536919]
88. Lawrence JK, Maher ER, Sheaves R, Grossman AB. Familial paraganglioma: a novel presentation of a case and response to therapy with radiolabelled MIBG. *Hormones (Athens).* 2004; 3:127–131. [PubMed: 16982587]
89. Lee SC, Chionh SB, Chong SM, Taschner PE. Hereditary paraganglioma due to the SDHD M11 mutation in a second Chinese family: a founder effect? *Laryngoscope.* 2003; 113:1055–1058. [PubMed: 12782822]
90. Leube B, Huber R, Goecke TO, Sandmann W, Royer-Pokora B. SDHD mutation analysis in seven German patients with sporadic carotid body paraganglioma: one novel mutation, no Dutch founder mutation and further evidence that G12S is a polymorphism. *Clin Genet.* 2004; 65:61–63. [PubMed: 15032977]
91. Liapis CD, Bellos JK, Halapas A, Lembessis P, Koutsilieris M, Kostakis A. Carotid body paraganglioma and SDHD mutation in a Greek family. *Anticancer Res.* 2005; 25:2449–2452. [PubMed: 16080474]
92. Lima J, Feijão T, Ferreira da Silva A, et al. High frequency of germline succinate dehydrogenase mutations in sporadic cervical paragangliomas in northern Spain: mitochondrial succinate dehydrogenase structure-function relationships and clinical-pathological correlations. *J Clin Endocrinol Metab.* 2007; 92:4853–4864. [PubMed: 17848412]
93. López-Jiménez E, de Campos JM, Kusak EM, et al. SDHC mutation in an elderly patient without familial antecedents. *Clin Endocrinol.* 2008 in press.
94. Ma RC, Lam CW, Chan WB, So WY, Tong SF, Chow CC, Cockram CS. A Chinese family with familial paraganglioma syndrome due to succinate dehydrogenase deficiency. *Hong Kong Med J.* 2007; 13:151–154. [PubMed: 17406045]
95. Maier-Woelfle M, Brändle M, Komminoth P, et al. A novel succinate dehydrogenase subunit B gene mutation, H132P, causes familial malignant sympathetic extraadrenal paragangliomas. *J Clin Endocrinol Metab.* 2004; 89:362–367. [PubMed: 14715873]
96. Mannelli M, Simi L, Ercolino T, et al. SDH mutations in patients affected by paraganglioma syndromes: a personal experience. *Ann N Y Acad Sci.* 2006; 1073:183–189. [PubMed: 17102085]
97. Mannelli M, Ercolino T, Giachè V, Simi L, Cirami C, Parenti G. Genetic screening for pheochromocytoma: should SDHC gene analysis be included? *J Med Genet.* 2007; 44:586–587. [PubMed: 17557926]
98. McDonnell CM, Benn DE, Marsh DJ, Robinson BG, Zacharin MR. K40E: a novel succinate dehydrogenase (SDH)B mutation causing familial phaeochromocytoma and paraganglioma. *Clin Endocrinol (Oxf).* 2004; 61:510–514. [PubMed: 15473885]
99. McWhinney SR, Pilarski RT, Forrester SR, Schneider MC, Sarquis MM, Dias EP, Eng C. Large germline deletions of mitochondrial complex II subunits SDHB and SDHD in hereditary paraganglioma. *J Clin Endocrinol Metab.* 2004; 89:5694–5699. [PubMed: 15531530]
100. McWhinney SR, Pasini B, Stratakis CA. International Carney Triad and Carney-Stratakis Syndrome Consortium. Familial gastrointestinal stromal tumors and germ-line mutations. *N Engl J Med.* 2007; 357:1054–1056. [PubMed: 17804857]
101. Mhatre AN, Li Y, Feng L, Gasperin A, Lalwani AK. SDHB, SDHC, and SDHD mutation screen in sporadic and familial head and neck paragangliomas. *Clin Genet.* 2004; 66:461–466. [PubMed: 15479192]
102. Milunsky JM, Maher TA, Michels VV, Milunsky A. Novel mutations and the emergence of a common mutation in the SDHD gene causing familial paraganglioma. *Am J Med Genet.* 2001; 100:311–314. [PubMed: 11343322]
103. Mora J, Cascón A, Robledo M, Catala A. Pediatric paraganglioma: an early manifestation of an adult disease secondary to germline mutations. *Pediatr Blood Cancer.* 2006; 47:785–789. [PubMed: 16304664]

104. Moreno Tejero ML, Pintor Trevejo M, Martín Ruiz C, Galán Gómez E. Pheochromocytoma associated with a paraganglion syndrome. *An Pediatr*. 2008; 68:527–529.
105. Neumann HP, Bausch B, McWhinney SR, et al. Freiburg-Warsaw-Columbus Pheochromocytoma Study Group. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med*. 2002; 346:1459–1466. [PubMed: 12000816]
106. Neumann HP, Pawlu C, Peczkowska M, et al. European-American Paraganglioma Study Group. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. *JAMA*. 2004; 292:943–951. [PubMed: 15328326]
107. Neumayer C, Moritz A, Asari R, et al. Novel SDHD germ-line mutations in pheochromocytoma patients. *Eur J Clin Invest*. 2007; 37:544–551. [PubMed: 17576205]
108. Ni Y, Zbuk KM, Sadler T, et al. Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes. *Am J Hum Genet*. 2008; 83:261–268. [PubMed: 18678321]
109. Niemann S, Müller U, Engelhardt D, Lohse P. Autosomal dominant malignant and catecholamine-producing paraganglioma caused by a splice donor site mutation in SDHC. *Hum Genet*. 2003; 113:92–94. [PubMed: 12658451]
110. Novosel A, Heger A, Lohse P, Schmidt H. Multiple pheochromocytomas and paragangliomas in a young patient carrying a SDHD gene mutation. *Eur J Pediatr*. 2004; 163:701–703. [PubMed: 15365827]
111. Ogawa K, Shiga K, Saijo S, Ogawa T, Kimura N, Horii A. A novel G106D alteration of the SDHD gene in a pedigree with familial paraganglioma. *Am J Med Genet*. 2006; 140:2441–2446. [PubMed: 17041923]
112. Papaspyrou K, Rossmann H, Fottner C, Weber MM, Mann W, Lackner KJ, Helling K. Malignant paraganglioma caused by a novel germline mutation of the succinate dehydrogenase D-gene - a case report. *Head Neck*. 2008; 30:964–969. [PubMed: 18213727]
113. Pasini B, McWhinney SR, Bei T, et al. Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. *Eur J Hum Genet*. 2008; 16:79–88. [PubMed: 17667967]
114. Peczkowska M, Cascon A, Prejbisz A, et al. Extra-adrenal and adrenal pheochromocytomas associated with a germline SDHC mutation. *Nat Clin Pract Endocrinol Metab*. 2008; 4:111–115. [PubMed: 18212813]
115. Persu A, Hamoir M, Grégoire V, et al. High prevalence of SDHB mutations in head and neck paraganglioma in Belgium. *J Hypertens*. 2008; 26:1395–1401. [PubMed: 18551016]
116. Petramala L, Cavallaro G, Polistena A, et al. Multiple catecholamine-secreting paragangliomas: diagnosis after hemorrhagic stroke in a young woman. *Endocr Pract*. 2008; 14:3406.
117. Pollard PJ, Brière JJ, Alam NA, et al. Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. *Hum Mol Genet*. 2005; 14:2231–2239. [PubMed: 15987702]
118. Renard L, Godfraind C, Boon LM, Vikkula M. A novel mutation in the SDHD gene in a family with inherited paragangliomas--implications of genetic diagnosis for follow up and treatment. *Head Neck*. 2003; 25:146–151. [PubMed: 12509798]
119. Ricketts C, Woodward ER, Killick P, Morris MR, Astuti D, Latif F, Maher ER. Germline SDHB Mutations and Familial Renal Cell Carcinoma. *J Natl Cancer Inst*. 2008; 100:1260–1262. [PubMed: 18728283]
120. Schiavi F, Boedeker CC, Bausch B, et al. European-American Paraganglioma Study Group. Predictors and prevalence of paraganglioma syndrome associated with mutations of the SDHC gene. *JAMA*. 2005; 294:2057–2063. [PubMed: 16249420]
121. Schiavi F, Savvoukidis T, Tralbalzini F, et al. Paraganglioma syndrome: SDHB, SDHC, and SDHD mutations in head and neck paragangliomas. *Ann N Y Acad Sci*. 2006; 1073:190–197. [PubMed: 17102086]
122. Simi L, Sestini R, Ferruzzi P, et al. Phenotype variability of neural crest derived tumours in six Italian families segregating the same founder SDHD mutation Q109X. *J Med Genet*. 2005; 42:e52. [PubMed: 16061558]

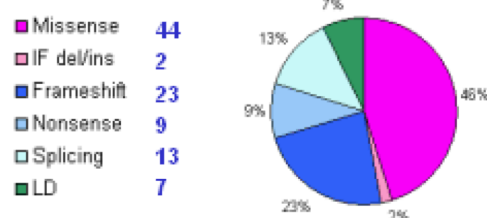
123. Srirangalingam U, Walker L, Khoo B, et al. Clinical manifestations of familial paraganglioma and pheochromocytomas in succinate dehydrogenase B gene mutation carriers. *Clin Endocrinol (Oxf)*. 2008; 69:587–596. [PubMed: 18419787]
124. Takahashi M, Yang XJ, McWhinney S, et al. cDNA microarray analysis assists in diagnosis of malignant intrarenal pheochromocytoma originally masquerading as a renal cell carcinoma. *J Med Genet*. 2005; 42:e48. [PubMed: 16061554]
125. Takekoshi K, Isobe K, Suzuki H, Nissato S, Kawakami Y, Kawai K, Yamada N. R46Q mutation in the succinate dehydrogenase B gene (SDHB) in a Japanese family with both abdominal and thoracic paraganglioma following metastasis. *Endocr J*. 2008; 55:299–303. [PubMed: 18362451]
126. Taschner PE, Jansen JC, Baysal BE, et al. Nearly all hereditary paragangliomas in the Netherlands are caused by two founder mutations in the SDHD gene. *Genes Chromosomes Cancer*. 2001; 31:274–281. [PubMed: 11391798]
127. Timmers HJ, Kozupa A, Eisenhofer G, et al. Clinical presentations, biochemical phenotypes, and genotype-phenotype correlations in patients with succinate dehydrogenase subunit B-associated pheochromocytomas and paragangliomas. *J Clin Endocrinol Metab*. 2007; 92:779–786. [PubMed: 17200167]
128. Timmers HJ, Pacak K, Bertherat J, et al. Mutations associated with succinate dehydrogenase D-related malignant paragangliomas. *Clin Endocrinol*. 2008; 68:561–566.
129. Vanharanta S, Buchta M, McWhinney SR, et al. Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma. *Am J Hum Genet*. 2004; 74:153–159. [PubMed: 14685938]
130. van Houtum WH, Corssmit EP, Douwes Dekker PB, et al. Increased prevalence of catecholamine excess and pheochromocytomas in a well-defined Dutch population with SDHD-linked head and neck paragangliomas. *Eur J Endocrinol*. 2005; 152:87–94. [PubMed: 15762191]
131. Velasco A, Palomar-Asenjo V, Gañan L, et al. Mutation analysis of the SDHD gene in four kindreds with familial paraganglioma: description of one novel germline mutation. *Diagn Mol Pathol*. 2005; 14:109–114. [PubMed: 15905695]
132. Young AL, Baysal BE, Deb A, Young WF Jr. Familial malignant catecholamine-secreting paraganglioma with prolonged survival associated with mutation in the succinate dehydrogenase B gene. *J Clin Endocrinol Metab*. 2002; 87:4101–4105. [PubMed: 12213855]
133. Zantour B, Guillaume B, Tissier F, Louvel A, Jeunemaitre X, Gimenez-Roqueplo AP, Bertagna X. A thyroid nodule revealing a paraganglioma in a patient with a new germline mutation in the succinate dehydrogenase B gene. *Eur J Endocrinol*. 2004; 151:433–438. [PubMed: 15476441]
134. Zbuk KM, Patocs A, Shealy A, Sylvester H, Miesfeldt S, Eng C. Germline mutations in PTEN and SDHC in a woman with epithelial thyroid cancer and carotid paraganglioma. *Nat Clin Pract Oncol*. 2007; 4:608–612. [PubMed: 17898811]
135. Bayley JP, Devilee P, Taschner PE. The SDH mutation database: an online resource for succinate dehydrogenase sequence variants involved in pheochromocytoma, paraganglioma and mitochondrial complex II deficiency. *BMC Med Genet*. 2005; 6:39. [PubMed: 16288654]
136. Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. *Am J Surg Pathol*. 2007; 31:1578–1585. [PubMed: 17895761]
137. Carvajal-Carmona LG, Alam NA, Pollard PJ, et al. Adult leydig cell tumors of the testis caused by germline fumarate hydratase mutations. *J Clin Endocrinol Metab*. 2006; 91:3071–3075. [PubMed: 16757530]
138. Matyakhina L, Freedman RJ, Bourdeau I, et al. Hereditary leiomyomatosis associated with bilateral, massive, macronodular adrenocortical disease and atypical cushing syndrome: a clinical and molecular genetic investigation. *J Clin Endocrinol Metab*. 2005; 90:3773–3779. [PubMed: 15741255]
139. Lima J, Teixeira-Gomes J, Soares P, Máximo V, Honavar M, Williams D, Sobrinho-Simões M. Germline succinate dehydrogenase subunit D mutation segregating with familial non-RET C cell hyperplasia. *J Clin Endocrinol Metab*. 2003; 88:4932–4937. [PubMed: 14557476]

140. Dannenberg H, Speel EJ, Zhao J, et al. Losses of chromosomes 1p and 3q are early genetic events in the development of sporadic pheochromocytomas. *Am J Pathol.* 2000; 157:353–359. [PubMed: 10934139]
141. Opocher G, Schiavi F, Vettori A, et al. Fine analysis of the short arm of chromosome 1 in sporadic and familial pheochromocytoma. *Clin Endocrinol (Oxf).* 2003; 59:707–715. [PubMed: 14974911]
142. Pollard PJ, Brière JJ, Alam NA, et al. Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. *Hum Mol Genet.* 2005; 14:2231–2239. [PubMed: 15987702]
143. Selak MA, Armour SM, MacKenzie ED, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. *Cancer Cell.* 2005; 7:77–85. [PubMed: 15652751]
144. Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer.* 2003; 3:721–732. [PubMed: 13130303]
145. Lee S, Nakamura E, Yang H, et al. Neuronal apoptosis linked to EglN3 prolyl hydroxylase and familial pheochromocytoma genes: developmental culling and cancer. *Cancer Cell.* 2005; 8:155–167. [PubMed: 16098468]
146. Masuoka J, Brandner S, Paulus W, et al. Germline SDHD mutation in paraganglioma of the spinal cord. *Oncogene.* 2001; 20:5084–5086. [PubMed: 11526495]
147. Braun S, Riemann K, Kupka S, Leistenschneider P, Sotlar K, Schmid H, Blin N. Active succinate dehydrogenase (SDH) and lack of SDHD mutations in sporadic paragangliomas. *Anticancer Res.* 2005; 25:2809–2814. [PubMed: 16080530]
148. Aguiar RC, Cox G, Pomeroy SL, Dahia PL. Analysis of the SDHD gene, the susceptibility gene for familial paraganglioma syndrome (PGL1), in pheochromocytomas. *J Clin Endocrinol Metab.* 2001; 86:2890–2894. [PubMed: 11397905]
149. Perren A, Barghorn A, Schmid S, Saremaslani P, Roth J, Heitz PU, Komminoth P. Absence of somatic SDHD mutations in sporadic neuroendocrine tumors and detection of two germline variants in paraganglioma patients. *Oncogene.* 2002; 21:7605–7608. [PubMed: 12386824]
150. Kytölä S, Nord B, Elder EE, et al. Alterations of the SDHD gene locus in midgut carcinoids, Merkel cell carcinomas, pheochromocytomas, and abdominal paragangliomas. *Genes Chromosomes Cancer.* 2002; 34:325–332. [PubMed: 12007193]
151. Sun HY, Cui B, Su DW, et al. LOH on chromosome 11q, but not SDHD and Men1 mutations was frequently detectable in Chinese patients with pheochromocytoma and paraganglioma. *Endocrine.* 2006; 30:307–312. [PubMed: 17526943]
152. van Nederveen FH, Korpershoek E, Lenders JW, de Krijger RR, Dinjens WN. Somatic SDHB mutation in an extraadrenal pheochromocytoma. *N Engl J Med.* 2007; 357:306–308. [PubMed: 17634472]
153. Astuti D, Morris M, Krona C, et al. Investigation of the role of SDHB inactivation in sporadic pheochromocytoma and neuroblastoma. *Br J Cancer.* 2004; 91:1835–1841. [PubMed: 15505628]
154. Montani M, Schmitt AM, Schmid S, et al. No mutations but an increased frequency of SDHx polymorphisms in patients with sporadic and familial medullary thyroid carcinoma. *Endocr Relat Cancer.* 2005; 12:1011–1016. [PubMed: 16322339]
155. Hui AB, Lo KW, Chan SY, Kwong J, Chan AS, Huang DP. Absence of SDHD mutations in primary nasopharyngeal carcinomas. *Int J Cancer.* 2002; 97:875–877. [PubMed: 11857371]
156. Habano W, Sugai T, Nakamura S, Uesugi N, Higuchi T, Terashima M, Horiuchi S. Reduced expression and loss of heterozygosity of the SDHD gene in colorectal and gastric cancer. *Oncol Rep.* 2003; 10:1375–1380. [PubMed: 12883710]
157. Morris MR, Maina E, Morgan NV, et al. Molecular genetic analysis of FH-1, FH, and SDHB candidate tumour suppressor genes in renal cell carcinoma. *J Clin Pathol.* 2004; 57:706–711. [PubMed: 15220362]
158. Pawlu C, Bausch B, Neumann HP. Mutations of the SDHB and SDHD genes. *Fam Cancer.* 2005; 4:49–54. [PubMed: 15883710]

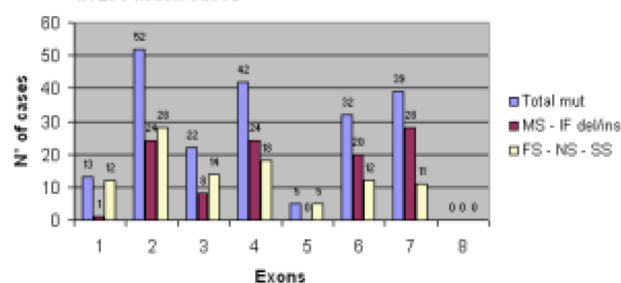
159. De Krijger RR, Petri BJ, Van Nederveen FH, Korpershoek E, De Herder WW, De Muinck Keizer-Schrama SM, Dinjens WN. Frequent genetic changes in childhood pheochromocytomas. *Ann N Y Acad Sci.* 2006; 1073:166–176. [PubMed: 17102083]

1.1 SDHB

98 germline mutations in 216 index cases

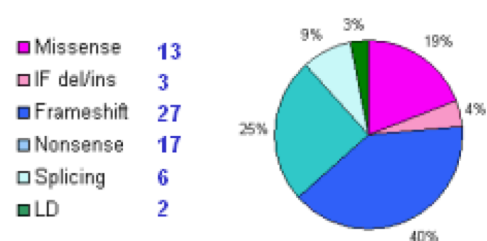


Distribution of SDHB point mutations identified in 205 index cases

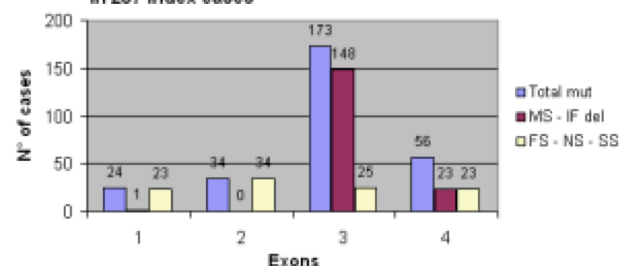


1.2 SDHD

68 germline mutations in 289 index cases

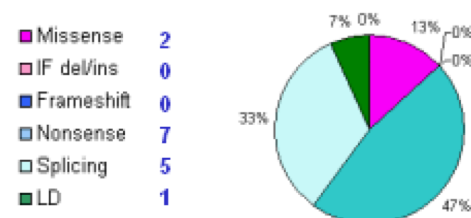


Distribution of SDHD point mutations identified in 287 index cases



1.3 SDHC

15 germline mutations in 19 carriers



Distribution of SDHC point mutations identified in 17 index cases

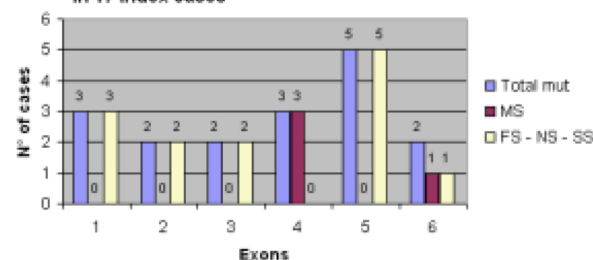
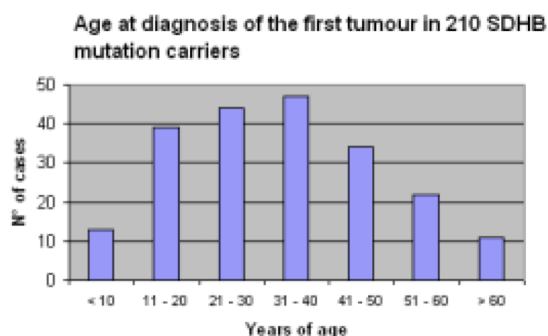


Figure 1. Spectrum of germline mutations identified in *SDHB* (1.1), *SDHD* (1.2) and *SDHC* (1.3) genes

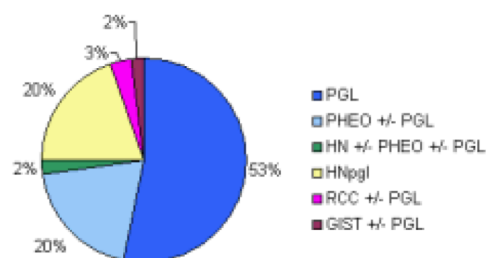
For each *SDH* gene, the left image shows numbers and percentages of the different types of mutations including missense (MS), in-frame deletion/insertion (IF del/ins), frame-shift (FS), nonsense (NS), splice-site (SS) and large genomic deletions (LD). The right histogram shows the distribution of point mutations along the coding exons of each gene (blue bar = total of mutations, purple bar = missense and in-frame insertion/deletion, light-yellow bar = truncating mutations).

2.1 SDHB

range: 7-76 yrs
median: 32
mean: 33.3

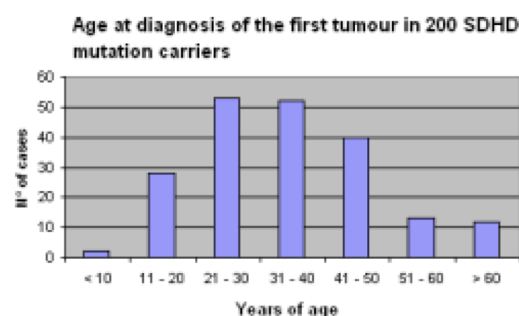


Phenotype of 264 SDHB affected carriers

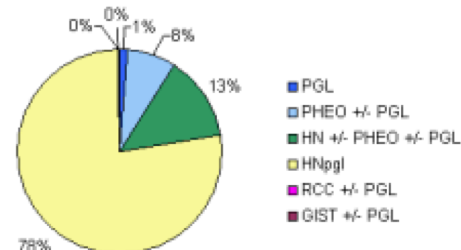


2.2 SDHD

range: 5-73 yrs
median: 33
mean: 34.9

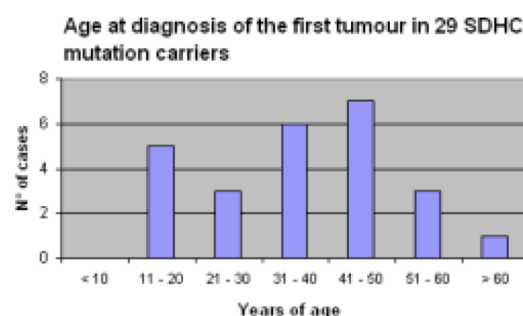


Phenotype of 395 SDHD affected carriers



2.3 SDHC

range: 13-73 yrs
median: 38
mean: 38.8



Phenotype of 30 SDHC affected carriers

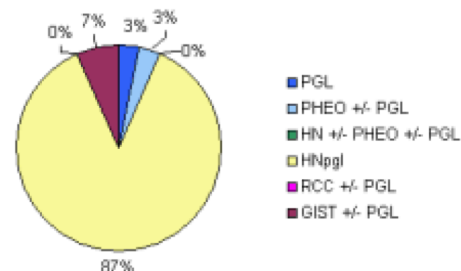


Figure 2. Clinical manifestations of *SDHB* (2.1), *SDHD* (2.2) and *SDHC* (2.3) affected carriers
For each *SDH* gene the left histogram shows the distribution of ages at diagnosis of the first tumour. The range, median and mean ages are also resumed. The right image shows the percentages of various tumour phenotypes, including extra-adrenal paraganglioma alone (PGL, blue), adrenal pheochromocytoma with or without extra-adrenal PGLs (PHEO +/- PGL, azure), head and neck paraganglioma alone (HNpgl, yellow), head and neck PGLs with PHEO and/or PGL (HN +/- PHEO +/- PGL, green), renal cell cancer (RCC, pink), gastrointestinal stromal tumours (GIST, purple) with or without (+/-) other neuroendocrine tumours.

SDH germline mutations in series of sporadic or unselected patients with adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma

Table 1

Data on the prevalence of *SDH* germline mutations in sporadic non syndromic PHEOs/PGLs have been derived from 11 studies in which the family history was clearly indicated or the study design was adequate for the purpose of this review. When the same research group published an increasing series of cases over the time, only the last publication has been considered for the calculation of the general prevalence (marked with #). "neg" = cases negative for mutations in the given gene. "nd" = analysis not done.

Tumor type	N° of cases	RET	VHL	SDHB	SDHC	SDHD	Tot SDH	References (population)
Sporadic PHEO-PGL	24	neg	neg	2 (8.3%)	0	0	2 (8.3%)	Astuti D et al. 2001 [11, 50] (English)
Sporadic PHEO-PGL 14 adrenal, 4 extra-adrenal	18	neg	neg	nd	nd	2 (11.1%)		Gimm O et al. 2000 [81] (German)
Sporadic PHEO-PGL - < 30 years (160)	13 (4.8%)	30 (11%)	12 (4.4%)			11 (4%)		
- adrenal (241)	4 (2.5%)	25 (15.6%)	8 (5%)			6 (3.7%)		
- extra-adrenal (30)	13 (5.4%)	26 (10.8%)	6 (2.5%)	nd		7 (2.9%)	23 (8.5%)	Neumann H et al. 2002 [105] (German, Polish)
- multiple tumours (26)	0 (0%)	4 (13.3%)	6 (20%)			4 (13.3%)		
	5 (19.2%)	12 (46.1%)	0 (0%)			4 (15.4%)		
Sporadic PHEO-PGL	304	neg	neg	16 (5.3%)	neg	13 (4.3%)	29 (9.5%)	Neumann H et al. 2004 [106] (German, Polish)
Sporadic PHEO-PGL	371	neg	neg	21 (5.7%)	0	21 (5.7%)	42 (11.3%)	# Schiavi F et al. 2005 [120] (German, Polish and other countries)
Sporadic PHEO-PGL adrenal (69)			2 (2.4%)	8 (9.5%)				
- benign (57)	84	0	2 (3.5%)	1 (1.7%)	nd	0	8 (9.5%)	Gimenez-Roqueplo AP et al. 2003 [80] (French)
- malignant (12)			0 (0%)	2 (16.7)				
extra-adrenal (15)			0 (0%)	5 (33.3%)				
Sporadic PHEO-PGL	258	1 (0.4%)	9 (3.5%)	18 (7%)	0	3 (1.2%)	21 (8.1%)	# Amar L et al. 2005 [46] (French)
Sporadic PHEO-PGL	213	0	6/136 (4.4%)	1/47 (2%)	nd	2/126 (1.6%)		Korpershoek E et al. 2006 [84] (Dutch)
Sporadic PHEO-PGL	18	0	0	0	0	0	0	Persu A et al. 2008 [115] (Belgian)
PHEO collected anonymously	35	2 (5.7%)	0	1 (2.8%)	nd	2 (5.7%)	3 (8.5%)	Cascón A et al. 2004 [33] (Spanish)

Tumor type	N° of cases	RET	VHL	SDHB	SDHC	SDHD	Tot SDH	References (population)
Total PHEO-PGLs negative for RET-VHL mutations	901			43/741 5.8%	0/661 0%	28/820 3.4%	9%	combined data

Table 2
***SDH* germline mutations in series of malignant adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma**

Data on the prevalence of *SDH* germline mutations among malignant PHEOs/PGLs have been derived from 4 studies giving a general frequency of 38% with a marked predominance of *SDHB* mutations. In two studies, together with deleterious mutations, 7 *vs* have been identified. However, giving their absence in normal controls and in other series of cases, a pathogenic role is suspected. “neg” = cases negative for mutations in the given gene. “nd” = analysis not done.

Tumor type	N° of cases	RET	VHL	NF1	SDHB	SDHC	SDHD	References (population)
Malignant PHEO-PGL					13 to 18* (30 to 41%)			
- adrenal (13)	44	nd	nd	nd	2 (15.4%)	nd	nd	Brouwers FM et al. 2006 [60] (NIH – USA) *5 cases with genetic variants
- extra-adrenal (29)					16 (55.2%)			
- uncertain (2)					0 (0%)			
Malignant PHEO-PGL					23 (42.6%)			Amar L et al. 2007 [47] (French)
- syndromic (5)					2 (40%)			
- sporadic (49)	54	0	1 (2%)	0	21 (42.8%)	nd	0	
- adrenal (29)			ns	ns	7 (24.1%)			
- extra-adrenal (25)			ns	ns	16 (64%)			
Malignant PHEO-PGL					1 (11%)			
- adrenal (5)	9	nd	nd	nd	0	nd	0	Isobe K et al. (2007) [86] (Japanese)
- extra-adrenal (4)					1 (25%)			
Malignant PHEO-PGL					6 to 7* (21 to 25%)		1–2* (3.6–7%)	
- adrenal (12)	28	nd	nd	nd	0	nd	2 (16.7%)	Klein RD et al. 2008 [83] (USA) *2 cases with genetic variants
- extra-adrenal (16)					7 (43.8)		0	
Total malignant PHEO/PGLs	135				49/135 36%		2/91 2%	combined data

Table 3
SDH germline mutations in series of patients with suspected genetic predisposition to adrenal (PHEO) or extra-adrenal (PGL) pheochromocytoma

Data on the prevalence of *SDH* germline mutations in cases suspected for a genetic predisposition giving the early age at onset, multiple or bilateral tumours or positive family history. "neg" = cases negative for mutations in the given gene. "nd" = analysis not done.

Phenotype	N° of cases	RET	VHL	SDHB	SDHC	SDHD	Tot SDH	References (population)
Paediatric PGL	3	0	0	3 (100%)	0	0	3 (100%)	Mora J et al. 2006 [103] (Spanish)
Paediatric PHEO	4	neg	neg	2 (50%)	0	0	2 (50%)	Astuti D et al. 2003 [51] (English)
Paediatric PHEO 9–18 years of age	10	2 (20%)	1 (10%)	0	nd	0	0	De Krijger RR et al. 2006 [159] (Dutch)
Multiple sporadic PHEO-PGL	26	5 (19.2%)	12 (46.1%)	0	nd	4 (15.4%)	4 (15.4%)	Neumann H et al. 2002 [105] (German, Polish)
Multiple sporadic PHEO-PGL	10	neg	neg	0	0	1 (10%)	1 (10%)	Astuti D et al. 2003 [51] (English)
Bilateral PHEO sporadic and familial	33	21 (63.6%)	2 (6%)	0	nd	1 (3%)	10% of cases neg. for RET - VHL	Korpershoek E et al. 2007 [85] (Dutch)
Familial PHEO adrenal and extra-adrenal	12	neg	neg	2 (17%)	0	0	2 (17%)	Astuti D et al. 2003 [51] (English)
Familial PHEO / PGL / HNPGL	5	neg	neg	3 (60%)	0	1 (20%)	4 (80%)	Astuti D et al. 2003 [51] (English)
Familial PHEO / PGL / HNPGL	5	nd	nd	5 (100%)	0	nd	5 (100%)	Bayley JP et al. 2006 [54] (Dutch and other countries)
Familial PHEO / PGL / HNPGL	3	0	1 (33.3%)	1 (33.3%)	0	1 (33.3%)	2 (66.6%)	Castellano M. et al. 2006 [66] (Italian)

Table 4
SDH germline mutations in series of cases with head and neck paragangliomas (HNPGL)

Data on the prevalence of *SDH* germline mutations in series of cases with HNPGL either sporadic (unique tumours), multiple or familial are derived from 8 studies analysing different populations outside the area of Low Countries. The last paper (marked with #) has been excluded from calculation of the general prevalence because data were not presented according with different phenotypes.

Phenotype	N° of cases	SDHB	SDHC	SDHD	Tot SDH	References (population)
HNPGL						
- familial (10)	3 (6.4%)	2# (4.3%)	7 (14.9%)	12 (25.5%)		Baysal BE et al. 2002. # Baysal BE et al. 2004 [55, 56] (US, Pittsburg and Los Angeles)
- multiple (5)	2 (20%)	1 (10%)	5 (50%)	8 (80%)		
- sporadic (32)	0	0	2 (40%)	2 (40%)		
	1 (3.1%)	1 (3.1%)	0	2 (6.3%)		
HNPGL						
- familial (3)	1 (5.9%)	1 (5.9%)	2 (11.8%)			Mhatre AN et al. 2004 [101] (US)
- sporadic (14)	1 (33.3%)	0	1 (33.3%)	2 (66.7%)		
	0	0	0	0		
HNPGL						
- familial (1)	4 (11.8%)	4 (11.8%)	4 (11.8%)			Astuti D et al. 2003 [51] (English)
- multiple (3)	0	0	1 (100%)	1 (100%)		
- sporadic (30)	34	0	3 (100%)	3 (100%)		
			0	0		
HNPGL						
- familial (10)	3 (8.8%)	11 (32.3%)	14 (41.2%)			Badenhop RF et al. 2004 [52] (Australian)
- multiple (1)	1 (10%)	0	8 (80%)	9 (90%)		
- sporadic (23)	0	1 (100%)	1 (100%)	1 (100%)		
	2 (8.7%)	2 (8.7%)	4 (17.4%)			
HNPGL						
- familial (4)	1 (4.3%)	1 (4.3%)	6 (26%)	8 (34.8%)		Fakhry N et al. 2008 [74] (French, Caucasian and Maghreb)
- multiple (3)	0	0	4 (100%)	4 (100%)		
- sporadic (16)	0	1 (33.3%)	2 (66.6%)	3 (100%)		
	1 (6.3%)	0	0	1 (6.3%)		
HNPGL						
- familial (4)	7 (17.5%)	5 (12.5%)	12 (30%)			Lima J et al. 2007 [92] (Spanish, Portuguese)
- sporadic (36)	40	0	3 (75%)	4 (100%)		
	6 (16.7%)	2 (5.5%)	8 (22.2%)			

Phenotype	N° of cases	SDHB	SDHC	SDHD	Tot SDH	References (population)
HNPGL		1 (5%)	1 (5%)	2 (10%)	4 (20%)	
- familial (1)		0	1 (100%)	0	1 (100%)	Schiavi F et al. 2006 [121] (Italian)
- multiple (2)	20	0	0	2 (100%)	2 (100%)	
- sporadic (17)		1 (5.8%)	0	0	1 (5.8%)	
HNPGL familial, multiple and sporadic (data no specified)	121	8 (6.6%)	5 (4.1%)	20 (16.5%)	33 (27.3%)	# Schiavi F et al. 2005 [120] (77% German, 23% other countries)
Sporadic HNPGL	168	11/168 6.5%	1/168 0.6%	4/168 2.4%	9.5%	
Multiple HNPGL	14	0/14 0%	0/14 0%	10/14 71.4%	71.4%	combined data
Familial HNPGL	33	5/33 15%	2/33 6%	22/33 66.6%	87.8%	

SDH germline mutations in series of cases with head and neck paragangliomas (HNPGL) from the Netherlands and Belgium

Table 5

Data on the prevalence of *SDH* germline mutations in series of cases with HNPGL either sporadic (unique tumours), multiple or familial belonging from the Netherlands and Belgium are derived from 5 studies. When the same research group published an increasing series of cases over the time, only the last publication has been considered for the calculation of the general prevalence (marked with #). “nd” = analysis not done.

Phenotype	N° of cases	SDHB	SDHC	SDHD	Tot SDH	References (population)
HNPGL						
- familial (32)	87	nd	nd	52 (59.7%)		Taschner P et al. 2001 [126] (Dutch) * the only negative family is linked to PGL2 locus
- multiple (10)				31* (96.9%)		
- sporadic (45)#				8 (80%)		
				13 (28.9%)		
HNPGL sporadic (no further specified)	95 #	2 (2.1%)	1 (1%)	24 (25.3%)	27 (28.4%)	Bayley JP et al. 2006 Taschner P et al. 2001 [54, 126] (Dutch)
HNPGL						
- familial (19)	57	nd	nd	32 (56.1%)		Dammenberg H et al. 2002 [69] (Dutch)
- multiple (10)				19 (100%)		
- sporadic (28)				7 (70%)		
				6 (21.4%)		
HNPGL						
- familial (12)	21	0	nd	11 (52.4%)	12 (57.1%)	Douwes Dekker PB et al. 2003 [71] (Dutch) * the only negative family is linked to PGL2 locus
- multiple (3)				11* (91.7%)	11 (91.7%)	
- sporadic (6)				0	0	
				1 (16.7%)	1 (16.7%)	
HNPGL						
- familial (6)	36	0	0	9 (25%)	16 (44.4%)	Persu A et al. 2008 [115] (Belgian)
- sporadic (30)				6 (100%)	6 (100%)	
				3 (10%)	10 (33.3%)	
Sporadic HNPGL	159	10/131 7.6%	1/125 0.8%	33/159 20.7%	29.1%	combined data
Familial HNPGL	69	0%	0%	67/69 97%	97%	

Table 6

Clinical manifestations of *SDHB* mutation carriers

Clinical manifestations of *SDHB*, *SDHD* and *SDHC* affected carriers. The first column shows the number of cases reported in each study and the selection criteria. When patients have been selected for PHEOs/PGL head and neck tumours were absent or not specified ("ns") as it was true for series of HNPGL cases where adrenal and extra-adrenal PGLs were absent or not specified ("ns"). With respect to HNPGL, the percentage reported for each paraganglia refers to the involvement of the organ with respect to the total number of tumours recorded. Carotid b. = carotid body. nos = no otherwise specified.

Number of cases	Age at first tumour	Adrenal pheo	Abdominal pgl	Thoracic pgl	Head and neck pgl	Multiple tumours	Malignant tumours	References (population)
32	31.3 (10-65)	9 (28.1%)	16 (50%)	3 (9.3%)	10 (31.2%)	9 (28.1%)	11 (34.4%)	Neumann H et al. 2004 [106] (German, Polish)
51	47 (7-68)	9 (17.6%)	34 (66.7%)	9 (17.6%)	14 (27.4%)	6 / 49 (12.2%)	18 / 48 (37.5%)	Benn D et al. 2006 [58] (Australian, French, US, English, German)
18*	28 (10-48)	6 (33.3%)	13 (72.2%)	2 (11.1%)	2 (11.1%)	3 (16.6%)	6 (33.3%)	Srirangalingam U et al. 2008 [123] (English) * including 2 relatives and 3 genetic variants
21 PHEO-PGL	33.6 (10-58)	7 (33.3%)	17 (80.9%)	ns	ns	3 (14.3%)	15 (71.4%)	Amar L et al. 2005 [46] (French)
15 HNPGL only	39 (21-66)	ns	ns	ns	67% carotid b. 13% jugular 0% tympanic 13% vagal	4 (27%)	6 (40%)	Schiavi F et al. 2005 [120] (German, Polish and other countries)
3 HNPGL	27 (22-32)	0	ns	ns	0% carotid b. 67% jugular 0% tympanic 33% vagal	0	0	Badenhof RF et al. 2004 [52] (Australian)
264	33.3 (7-76)	12%	(abdominal in 45% of cases, thoracic in 5%, both in 66% 4%, nos in 11% of cases)		25%	33%	41%	present work

Table 7

Clinical manifestations of *SDHD* mutation carriers

Clinical manifestations of *SDHB*, *SDHD* and *SDHC* affected carriers. The first column shows the number of cases reported in each study and the selection criteria. When patients have been selected for PHEOs/PGL head and neck tumours were absent or not specified ("ns") as it was true for series of HNPGL cases where adrenal and extra-adrenal PGLs were absent or not specified ("ns"). With respect to HNPGL, the percentage reported for each paraganglia refers to the involvement of the organ with respect to the total number of tumours recorded. Carotid b. = carotid body. nos = no otherwise specified.

Number of cases	Age at first tumour	Adrenal Pheo	Abdominal pgl	Thoracic pgl	Head and neck pgl	Multiple tumours	Malignant tumours	References (population)
34	32.4 (5-60)	18 (52.9%)	7 (20.6%)	6 (17.6%)	27 (79.4%)	25 (73.5%)	0	Neumann H et al. 2004 [106] (German, Polish)
28	31 (7-73)	2 (7.1%)	5 (17.8%)	3 (10.7%)	25 (89.3%)	8 / 27 (29.6%)	2 / 26 (7.7%)	Benn D et al. 2006 [58] (Australian, French, US, English, Canadian)
18	39 (14-69)	3 (16.6%)	3 (16.6%)	2 (11.1%)	16 (88.9%) 79% carotid b. 9% jugular 12% vagal	15 (83.3%)	0	Simi L et al. 2005 [122] (Italian carriers of the fonder mut p.Gln109X)
11 PHEO-PGL	31.2 (17-59)	5 (45.4%)	7 (63.6%)	ns	ns	4 (36.3%)	0	Amar L et al. 2005 [46] (French)
57 HNPGL	34.2 (8-60)	6 (10.5%)	ns	ns	84.5% carotid body unilateral or bilateral	32 (56.1%)	4 (7%)	Astrom CK et al. 2003 [49] (21 from US, 1 from Canada, 1 from Turkey)
42 HNPGL only	36 (13-67)	ns	ns	ns	83% carotid b. 19% jugular 10% tympanic 2% vagal	24 (57%)	0	Schiavi F et al. 2005 [120] (German, Polish and other countries)
40 HNPGL	45.8	7 (17.5%)	1 (2.5%)	0	85% carotid b. 32.5% jugulo-tympanic 47.5% vagal	20 (50%)	0	van Houtum WH et al. 2005 [130] (Dutch)
19 HNPGL Fam, only	37.3	ns	ns	1 (5.3%)	66% carotid b. 12% jugular 6% tympanic 16% vagal	17 (89.5)	0	Dammenberg H et al. 2002 [69] (Dutch)
13 HNPGL	37.6 (18-69)	1 (7.7%)	1 (7.7%)	2 (15.4%)	74% carotid b. 7% jugular 7% vagal 11% other pgl	10 (76.9%)	0	Fish JH et al. 2007 [75] (Austrian)
11 HNPGL	36.4 (14-65)	1 (9%)	ns	ns	82% carotid b. 18% jugular 0% tympanic 27% vagal	4 (36.3%)	0	Badenhop RF et al. 2004 [52] (Australian)
395	35 (5-73)	14-16%	12-14%		91%	79%	5%	present work

Table 8

Clinical manifestations of *SDHC* mutation carriers

Clinical manifestations of *SDHB*, *SDHD* and *SDHC* affected carriers. The first column shows the number of cases reported in each study and the selection criteria. When patients have been selected for PHEOs/PGL head and neck tumours were absent or not specified ("ns") as it was true for series of HNPGL cases where adrenal and extra-adrenal PGLs were absent or not specified ("ns"). With respect to HNPGL, the percentage reported for each paraganglia refers to the involvement of the organ with respect to the total number of tumours recorded. Carotid b. = carotid body. nos = no otherwise specified.

Number of cases	Age at first tumour	Adrenal Pheo	Abdominal pgl	Thoracic pgl	Head and neck pgl	Multiple tumours	Malignant tumours	References (population)
22	46 (13-73)	0	0	0	22 (100%) 59% carotid b. 27% jugular 9% tympanic 9% vagal	2 (9%)	0	Schiavi F et al. 2005 [120] (German, Polish and other countries)
30	39 (13-73)	1 (33%)	3 (10%)	0	26 (87%)	8 (27%)	1 (3%)	present work

Table 9

***SDH* somatic point mutations and deletions (LOH) in pheochromocytomas (PHEO) and paragangliomas (PGL). When possible, samples from carriers of *SDH* germline mutations have been removed**

Results of 17 studies dealing with the search for somatic mutations and/or deletions (mainly loss-of-heterozygosity = LOH at microsatellite analysis) at *SDH* loci in HNPGLs, adrenal PHEOs and extra-adrenal PGLs. "nd" = analysis not done.

Tumour type	N° of samples	SDHB		SDHC		SDHD		Notes	References
		mut	LOH	mut	LOH	mut	LOH		
CNS-PGL	22	nd	nd	nd	nd	0	nd	Apparently sporadic pgl's of the cauda equina	Masuoka J et al. 2001 [146]
HNPGL	78	nd	nd	nd	nd	0	nd	Tumours from 57 cases (32 with germline <i>SDHD</i> mut)	Dannenberg H et al. 2002 [69]
HNPGL	30	0	nd	0	nd	0	nd	Tumours from cases negative for germline <i>SDHB-D</i> mut	Astuti D et al. 2003 [51]
HNPGL	14	0	nd	0	nd	0	nd	Tumours from cases negative for germline <i>SDHB-C-D</i> mut	Mhate AN et al. 2004 [101]
HNPGL	17	1/17	nd	0	nd	1/17	17 (100%)	Apparently sporadic hnpgl's 3 of which malignant	Braun S et al. 2005 [147]
PHEO - PGL	134	nd	nd	nd	nd	0	nd	Tumours from 126 cases (2 with germline <i>SDHD</i> mut)	Dannenberg H et al. 2005 [70]
PHEO	30	0	nd	nd	nd	0	nd	Tumours from cases negative for germline <i>SDHB-C-D RET</i> and <i>VHL</i> mut (<i>SDHB-D</i> promoter methylation was also negative)	Cascón A et al. 2004 [33]
PHEO	24	0	21/36* (58%)	0	nd	0	33%	Tumours from 24 sporadic cases (1 with a germline <i>SDHB</i> mut) *36 further analysed in 2004	Astuti D et al. 2001 [12, 50]
PHEO	20	nd	nd	nd	nd	0	nd	Tumours from cases negative for germline <i>SDHD</i> mut	Aguiar R et al. 2001 [148]
PHEO - PGL	16	nd	nd	nd	nd	1/16 (6%)	11 (69%)	Tumours from cases negative for germline <i>SDHD</i> mut	Gimm O et al. 2000 [81]
PHEO - PGL	18	nd	nd	nd	nd	0	1/3 (33.3%) 1/3 (33.3%)0/2	Pheochromocytomas (9) Sympathic PGLs (4) Para-sympathic PGLs (4)	Perren A et al. 2002 [149]
PHEO - PGL	44	nd	nd	nd	nd	0/18 0/3	9/30 (30%) 1/6 (17%)	37 sporadic pheos 7 sporadic abdominal pgl's	Kytölä S et al. 2002 [150]
PHEO - PGL	26	nd	9 (35%)	nd	nd	nd	7 (27%) all benign adrenal	Tumours from cases negative for germline <i>SDHB-D</i> mut	Gimenez-Roqueplo AP et al. 2003 [80]
PHEO - PGL	35	nd	nd	nd	nd	0	6/19 (31.6%) 2/6 (33.3%)	25 sporadic pheos 10 sporadic extra-adrenal pgl's	Sun HY et al. 2006 [151]

Tumour type	N° of samples	SDHB		SDHC		SDHD		Notes		References
		mut	LOH	mut	LOH	mut	LOH			
PGL	23	1/23 (4%)	nd	nd	nd	0	nd	Tumours from cases negative for germline <i>SDHB-D</i> mut		Korpershoek E et al. 2007 [85]

Table 10
SDH somatic point mutations and deletions (LOH) in tumour samples other than pheochromocytomas and paragangliomas

Results of 11 studies dealing with the search for somatic mutations and/or deletions (mainly loss-of-heterozygosity = LOH at microsatellite analysis) at *SDH* loci in a variety of tumours known to be characterized by 1p or 11q LOH or related to the “paraganglioma-pheochromocytoma syndrome” such as renal cell cancers.

Tumour type	N° of samples	SDHB		SDHC		SDHD		Notes	References
		mut	LOH	mut	LOH	mut	LOH		
Neuroendocrine tumours	25	nd	nd	nd	nd	0/18 0/7	5/8 (62.5%) nd	Midgut carcinoids (18) Merkel cell skin carcinomas (7)	Kytölä S et al. 2002 [150]
Neuroendocrine tumours	35	nd	nd	nd	nd	0/8 0/6 0/21	3/4 (75%) 1/3 (33%) 4/14 (29%)	Nets lung (8) Nets gastro-intestinal (6) Nets pancreas (21)	Perren A et al. 2002 [149]
Medullary thyroid ca.	35	0	8/30 (27%)	0	nd	0	1/24 (4.2%)	22 sporadic 13 from MEN2A patients	Montani M et al. 2005 [154]
Parathyroid adenomas	10	nd	nd	nd	nd	0	0		Perren A et al. 2002 [149]
Neuroblastomas	98	nd	nd	nd	nd	0/67 2/31 (6.4%)	20/67 (30%) 8/31 (26%)	67 primary tumours 31 cell lines	De Preter K et al. 2004 [32]
Neuroblastomas	46	0	unk	nd	nd	nd	nd	46 primary tumours	Astuti D et al. 2004 [153]
Nasopharyngeal carcinomas	50	nd	nd	nd	nd	0	22/43	43 primary tumours 4 cell lines 3 xenografts	Hui AB et al. 2002 [155]
Burkitt's lymphomas	9	nd	nd	nd	nd	0	unk	5 primary tumours 4 cell lines	Hui AB et al. 2002 [155]
Gastrointestinal cancers	111	nd	nd	nd	nd	unk	5/35 (14%) 5/40 (13%)	Colorectal cancers (52) Gastric cancers (59) Full paper not available	Habano W et al. 2003 [156]
Renal cell tumours	95	0	nd	nd	nd	0	nd	65 clear cell (35 < 50 yrs), 14 oncocytoma, ⁹ oncocytic-papillary, 3 papillary, 2 granular cell, 2 mixed	Vanharanta S et al. 2004 [129]
Renal cell tumours	29	0	1/18 (5.5%)	nd	nd	nd	nd	25 clear cell, 4 oncocytoma	Morris MR et al. 2004 [157]